Assessment of Coronary Heart disease In Low Likelihood patients with End Stage kidney disease (ACHILLES)

Comparison between Coronary Computed Tomography Angiography and Myocardial Perfusion Imaging

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Statement of originality

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Abstract

Purpose: To evaluate the diagnostic performance of Coronary Computed Tomography Angiography (CCTA) in predicting Myocardial Perfusion Scintigraphy (MPS) perfusion defects in low likelihood patients with End Stage Renal Disease (ESRD) awaiting transplant.

Materials and Methods: In total, 131 consecutive patients with ESRD awaiting transplant were prospectively enrolled in this study (86 men; 54±9years). All patients underwent MPS as per standard of care and in addition non-enhanced CT for calcium scoring (CAC score) and Coronary Computed Tomography Angiography (CCTA).

Results: The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CAC score in predicting MPS perfusion defects were 88%, 35%, 28% and 92%, respectively.
The sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the patient level were 55%, 87%, 57% and 87%, respectively, and 48%, 92%, 41% and 94% at the vessel level. The diagnostic performance of CCTA in predicting MPS perfusion defects improved when patients with CAC score higher than 1000 (15/70, 21%) were excluded from the analysis. In patients with positive CAC score up to 1000 sensitivity, specificity, PPV and NPV at the patient level were 60%, 93%, 75% and 86% respectively. These were 53%, 91%, 36% and 95%, respectively, at the vessel level.

Conclusion: Non-enhanced CT for CAC score and CCTA can be considered useful diagnostic tools in the ESRD population, particularly in identifying patients without coronary artery disease. This approach however had limitations in the presence of high CAC score.

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List of Abbreviations

ACCF: American College of Cardiology Foundation

ACS: Acute Coronary Syndrome

AHA: American Heart Association

AMI: Acute Myocardial Infarction

CABG: Coronary Artery Bypass Grafting

CAC: Coronary Calcium Scoring

CAD: Coronary Artery Disease

CCTA: Coronary Computed Tomography Angiography

CKD: Chronic Kidney Disease

CVD: Cardiovascular Disease

ESRD: End-Stage Renal Disease

HU: Hounsfield Unit

LV: Left Ventricle

LVH: Left Ventricular Hypertrophy

MACE: Major Acute Cardiovascular Event

MPI: Myocardial Perfusion Imaging

MPS: Myocardial Perfusion Scintigraphy

NPV: Negative Predictive Value

PCI: Percutaneous Coronary Intervention

PPV: Positive Predictive Value

PTH: Parathyroid Hormone

VSMC: Vascular Smooth Muscle Cells

Chapter 1: Rationale and Aims of this Thesis

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in end stage renal disease (ESRD) patients . This includes ESRD patients who receive a renal transplant. Therefore, in the attempt to reduce cardiovascular events during the preoperative period and after transplantation, screening for coronary artery disease (CAD) in ESRD patients being considered for renal transplantation is common clinical practice (2).

There are four main published guidelines for the preoperative cardiac evaluation of renal transplant candidates (3-6). Each of these guidelines, however, proposes slightly different criteria. The overall agreement amongst guidelines is poor and recommendations are at times inconsistent between guidelines (this will be discussed in detail in section 2.5.6). In Europe and the United States, myocardial perfusion scintigraphy (MPS) is the most widely used standard of care test to screen ESRD patients for CVD (7). However, it has been reported that the sensitivity of MPS in the detection of angiographically defined CAD was as low as 60% in dialysis patients (8). A potential explanation may be that concomitant conditions are often found in ESRD patients, such as left ventricular hypertrophy, or relative insensitivity to pharmacological stressors such as adenosine used for MPS imaging (discussed in section 2.6).

The overarching hypothesis of this thesis is that non-invasive anatomical imaging of the coronary arteries, which does not require administration of a pharmacological stressor and is not substantially affected by left ventricular hypertrophy, may represent a valuable tool for cardiovascular screening in ESRD patients.

The aims of this work were to compare coronary artery calcium (CAC) score (Aim 1) and coronary computed tomography angiography (CCTA) (Aim 2) with MPS for the diagnosis of CAD in patients with ESRD. We have evaluated the diagnostic performance of a CAC score/CCTA approach using MPS as the reference standard.

Chapter 2: Renal and Cardiovascular Disease

2.1 Definitions of End Stage Renal Disease (ESRD) and Chronic Kidney Disease (CKD)

End Stage Renal Disease (ESRD) is characterized by irreversible or nearly complete loss of renal function and represents the final stage of chronic kidney disease (CKD). CKD is a progressive loss of renal function due in 75% of cases to diabetes, hypertension or glomerulonephritis. CKD occurs either when there is a structural or functional abnormality of the kidney for at least 3 months with or without decrease of the estimated glomerular filtration rate (eGFR), or when the eGFR decreases to <60ml/min/1.73 m^2 (National Kidney Foundation, https://www.kidney.org/)(9).

eGFR is an estimate of the glomerular filtration rate – a measure of the excretory function of the kidney. In order to calculate the eGFR an estimating equation is required. The Modification of Diet in Renal Disease (MDRD) Study equation is one of the most widely used equations for estimating GFR in patients age 18 and over. This formula estimates GFR adjusted for serum creatinine, age, ethnicity, and gender and because the results are normalized to 1.73 m^2 body surface area, it does not require weight or height variables (10).

Proteinuria occurs as a result of the damage to the glomeruli and indicates presence of serum proteins in the urine. Proteins in the blood, like albumin, are too large to pass through the glomeruli into the urine. When the glomeruli are damaged, proteins of various sizes pass through them and are excreted in the urine.

It is widely accepted that proteinuria (and even more albuminuria) is a predictor of cardiovascular disease including ischaemic heart disease, stroke and hypertension in the general population (11). According to the Steno hypothesis (12) urinary protein excretion reflects localised subclinical renal disease and also a more generalised vascular endothelial dysfunction which is part of the atherosclerotic process (section 2.2)

CKD has five stages:

- Stage 1: GFR ≥ 90 ml/min/1.73 m^2

- Stage 2: GFR 60 – 89 ml/min/1.73 m^2
- Stage 3: GFR 30 – 59 ml/min/1.73 m^2
- Stage 4: GFR 15 – 29 ml/min/1.73 m^2
- Stage 5: GFR < 15 ml/min/1.73 m^2 or End Stage Renal Disease (ESRD)

For the definition of CKD in stage 1 and 2, structural or urinary abnormalities are also required. For patients in Stage 5 CKD or ESRD, renal replacement therapy is required in the form of either renal transplant or dialysis.

2.2. ESRD and Cardiovascular disease

The primary cause of mortality and morbidity in the ESRD population is CVD. The most common causes of cardiovascular death in ESRD are CAD, heart failure and arrhythmia (13). Despite an increase in life expectancy of ESRD patients related to the introduction of dialysis treatment, the mortality rates are still very high in these patients (14). An elevated cardiac mortality also persists after renal transplantation, particularly in the first year when the graft is still functional (15).

A variety of patient-related and dialysis-related factors have been shown to accelerate the atherosclerosis process in this population (16). The prevalence of atherosclerotic CAD in the ESRD population is thought to be greater than in age-matched controls and higher than it can be explained based on the conventional Framingham risk factors alone (1, 16).

There is substantial evidence of a negative correlation between glomerular filtration and cardiovascular disease. As the glomerular filtration decreases, the incidence of cardiovascular disease (CVD) increases independently from other risk factors (17, 18).

Furthermore, there is a strong association between the entity of microalbuminuria and the occurrence of cardiovascular events (19), perhaps through the association of microalbuminuria with endothelial dysfunction, which is one of the early stages of the atherosclerotic process in the vessel walls. In particular, endothelial dysfunction could directly influence albuminuria by increasing glomerular pressure and glomerular membrane permeability. Endothelial dysfunction can also indirectly influence

permeability by inflammatory mechanisms. As a result of impaired renal function, there is accumulation of uraemic toxins which, together with traditional cardiovascular risk factors (hypertension, diabetes, cigarette smoking and dyslipidaemia), play an important role in the induction of endothelial dysfunction (18). Renal impairment is typically associated with an increase of inflammatory biomarkers and chronic inflammation plays an important role in the atherosclerosis process. The atheroma is an active cellular lesion and many of the cells contained in the lesion facilitate inflammation, or result from inflammation (20). Inflammation is also one of the most important determinants of plaque "vulnerability", i.e. its susceptibility to rupture or erode as well as its thrombogenic potential , (12, 21). The plasma accumulation of uraemic toxins (partially removed by dialysis) together with dialysis-related factors results in an increase in the concentration plasma pro-inflammatory cytokines as well as other inflammatory biomarkers (22, 23) (Figure 1).

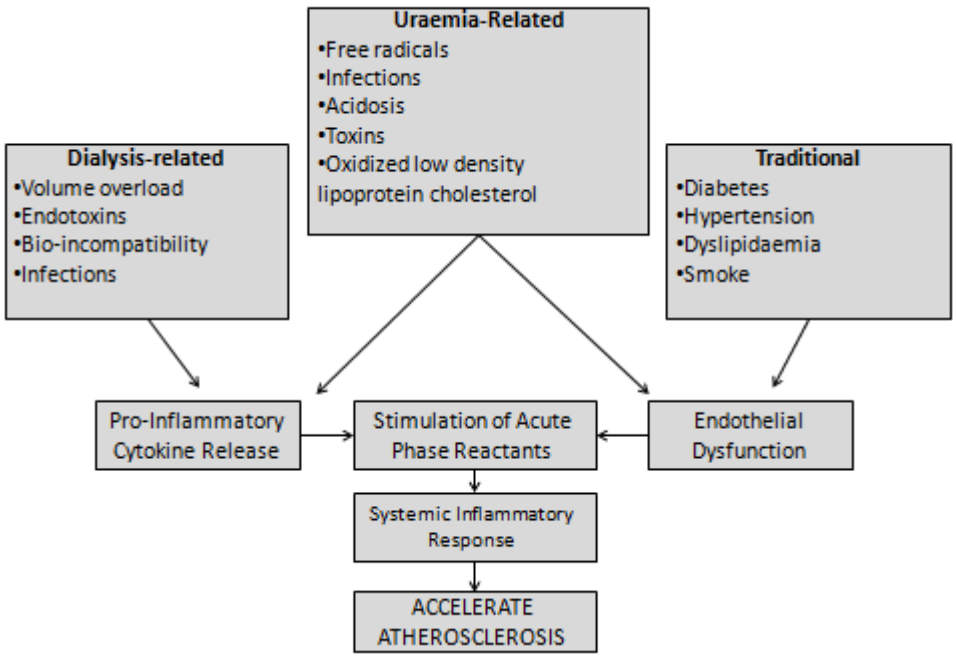

Figure 1: Mechanisms by which traditional cardiovascular risk factors combined with uraemia-related and dialysis-related risk factors induce a systemic inflammatory response. Modified from (18).

Renal impairment and microalbuminuria are associated with a range of lipid abnormalities (24). In this population the lipoprotein metabolism is compromised and this may result, especially in the most advanced stages, in the development of severe dyslipidaemia (25). In particular, there is a decrease of the HDL and HDL2 cholesterol known to be protective against CVD and there is an increase of triglycerides and VLDL cholesterol. Derangements of the lipid profiles can be described as below:

- Hypertriglyceridaemia: hypertriglyceridaemia [due to accumulation of VLDL and remnant lipoproteins such as intermediate-density lipoprotein (IDL)] is one of the most common abnormalities in CKD patients (26, 27) showing the highest values in dialysis patients (25). Delayed catabolism is the predominant mechanism responsible for increased concentration of triglycerideride lipoproteins in this population (28). The reason for diminished catabolic rate is the reduction of the lipoprotein lipase activity which is likely to be caused by a down-regulation of the enzyme's gene (29) and the presence of lipase inhibitors (30). Furthermore patients with CKD suffer from insulin resistance and this will promote hepatic VLDL production(31-33).

- Low density lipoprotein (LDL): Plasma total cholesterol in CKD population varies and it is usually normal or reduced; only occasionally this can be elevated in ESRD patients (25). The degree of proteinuria is a significant factor that influences the levels of plasma cholesterol-rich lipoproteins (25). The absence of heavy proteinuria in CKD does not significantly affect gene expressions of the rate-limiting enzyme for cholesterol biosynthesis (HMG-CoA reductase) or the rate-limiting enzyme for cholesterol catabolism and conversion to bile acids (7a-hydroxylase) (34). Hepatic LDL receptors mediate the cholesterol uptake and are not altered in absence of proteinuria (34).

In contrast, patients with nephrotic range proteinuria exhibit an acquired LDL-receptor deficiency (35). Studies in animals with experimental nephrosis revealed an upregulation of HMG-CoA reductase (36) as well as a

relative reduction of cholesterol 7a-hydroxylase (37). All the aforementioned mechanisms in concert may result in the increase of LDL blood levels in patients with proteinuria.

- High density lipoprotein (HDL): HDL proteins play a key role in the homeostasis of cholesterol and protection against atherosclerosis. They are responsible for the reverse cholesterol transport (transport of excess cholesterol from the arterial wall to the liver for excretion) and, moreover, inhibit inflammation and platelet adhesion(38). Patients with CKD have, generally, reduced plasma HDL cholesterol levels compared to individuals with normal renal function (39-41) and multiple mechanisms are involved:

1) Decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL) (41).

2) Diminished activity of lecithin-cholesterol acyltransferase (LCAT) (the enzyme responsible for the esterification of free cholesterol in HDL particles) (29, 42).

3) Increased activity of cholesteryl ester transfer protein (whose role is the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins thus reducing the serum concentrations of HDL-cholesterol) (43).

4) HDL particles from individuals with CKD have less effective antioxidative and anti-inflammatory function (44, 45).

5) The type of membrane and dialysate used in haemodialysis procedure may also influence the HDL-cholesterol levels (46, 47), in particular a low-flux instead of high flux membranes and the use of acetate dialysate are associated with a decrease of the HDL-cholesterol values (48, 49).

Carbohydrate metabolism disorders are also common in ESRD patients. Diabetes mellitus is present in a large group of patients on dialysis as one of the most common cause of ESRD. However, non-diabetic patients can also develop glucose intolerance (50), probably due to peripheral insulin resistance mainly resulting from uraemic toxins. Insulin resistance may contribute to the high cardiovascular morbidity and mortality in this population (51, 52).

Hypertension is very common in the ESRD population and its prevalence can range from 60% to 100% depending on the cause and severity of CKD (13).
It has been reported that high systolic blood pressure (>180 mmHg) as well as low systolic blood pressure (<100 mmHg) are associated with increased mortality in this population (53). CKD and high blood pressure are related in two ways:
1) High blood pressure is one of the leading causes of CKD and it still remains the second most common cause of ESRD after diabetic nephropathy (54). High blood pressure cannot only play a solitary role in the development of CKD but it has also been shown that coexistent hypertension (even mild-to-moderate blood pressure elevations) has an important role in the progression of most chronic kidney diseases (55, 56), including diabetic nephropathy.
2) High blood pressure can also represent a complication of CKD and there are several causes for this(57):
- Impaired sodium excretion resulting in expansion of the extracellular fluid compartment (57).
- Direct vasoconstriction effect due to activation of the renin-angiotensin system, sympathetic activation and increased production of endothelin (57).
- Loss of vasoconstriction effect due to nitric oxide and kinins (57).
- Imbalance between vasodilator and vasoconstrictor prostaglandins (58).

CKD patients, and nearly all those with ESRD who are on dialysis, are at risk of developing anaemia. As haemoglobin concentrations decrease to less than 11 g/dL there is a corresponding increase in the rate of hospitalisation and mortality in patients with CKD (59). The interaction between anaemia and renal failure is complex and multifactorial (60), the most common causes include:
1) Erythropoietin (EPO) deficiency: approximately 90% of the EPO is produced by the kidneys under hypoxic stimulation resulting into erythropoiesis stimulation (61). Damaged kidneys are unable to produce adequate EPO as result of hypoxia (61).

2) Systemic inflammation: inflammation together with microvascular disease (especially in diabetes patients) stimulates the production of inflammatory mediators (such as interleukins and tissue necrosis factor) and these can blunt the effect of the EPO on the bone marrow (62).
Other causes are shortened red cell life span and haemolysis (secondary to uraemic toxins accumulation), vitamin deficiencies, iron deficiency, and hyperuricaemia (leading to bone marrow suppression) (63).

The clinical consequences of anaemia depend on the severity of the oxygen reduction and the adaptive response to this change (64). There is an initial adaptive increase of the cardiac output that can become maladaptive as a result of stimulation of the left ventricular (LV) growth leading to left ventricular hypertrophy (LVH) and LV dilatation (65). Another important aspect in which anaemia can play a role (together with reduced vasodilator, microvascular disease and supply and demand mismatch due to LVH), is the occurrence of angina without CAD, seen in about 70% of patients with ESRD (8, 66).

It is worth noting that the presence of chest pain does not correlate with the presence and extent of CAD (7). It has been shown that the presentation of acute and chronic ischaemia can differ quite dramatically between ESRD and non-ESRD populations, which includes patients hospitalised with acute myocardial infarction (AMI) (67). In this regard, among ESRD patients on dialysis who are diagnosed with an AMI only 44.4% presented with acute chest pain as a symptom, compared to 68.3% in the non-ESRD population (p<0.0001) (67).

ESRD patients with chronic, stable CAD documented angiographically tend to have no symptoms too (68). In fact, in three studies (69-71), dialysis patients with angiographically documented CAD had no symptoms in 75%, 74% and 67% of the cases, respectively. The lack of symptoms is mainly attributed to diabetes and uraemic neuropathy (68). Moreover, ESRD patients generally have a sedentary lifestyle due to reduced exercise capacity from muscle

fatigue, anaemia and generalised feeling of illness after dialysis. These factors, secondary to rapid fluid and electrolyte shifts related to the dialysis treatment, contribute greatly to the lack of symptoms.

2.3. Uraemic Cardiomyopathy

There are different and confusing terms to define this condition. In practice, uraemic cardiomyopathy is the result of the influence of the pathological renal function on the myocardium that ultimately leads to LVH. LVH is defined as an increase in the mass of the LV, which can be secondary to an increase in wall thickness; normal ranges for septal wall thickness are 0.6-1.0 cm in men and 0.6-0.9 in women (72). LVH in ESRD is the result of pressure and volume overload as well as the uraemic state. LVH is indeed the first and most common cardiac adaptation in CKD and it is present in up to 75% of this population (73-75).

LVH can be present also in subjects with modest CKD, and importantly it is an independent predictor of survival in these patients (76-78).

LVH is the adaptive response to a variety of physiological and pathological stresses resulting in the enlargement of myocytes. The consequence of this is an initial normalisation of the wall tension in order to maintain the systolic function (15). In the very early stage, LVH is a beneficial adaptive response. Evidence exists, however, that hypertrophied hearts are more prone to injury and ventricular dysfunction (79), as LVH may initiate a cascade of detrimental maladaptative changes. In advanced stages the LV can be dilated with systolic and diastolic dysfunction (80, 81), ultimately resulting in heart failure (82).

It has been shown that capillary growth in the uraemic heart does not increase with myocyte hypertrophy (83, 84) and this results in a greater diffusion distance between the capillary and the centre of the myocyte. This translates into greater susceptibility of the myocardium to ischaemic damage (85).

Uraemia increases the activation and proliferation of cardiac interstitial fibroblasts (86-88) with the deposition of collagen fibres between capillaries and myocytes (myocardial fibrosis). Fibrosis is another common change that occurs during CKD (89), as confirmed in both experimental models (88, 90, 91) and post-mortem studies (92). Fibrosis plays a role in the progression of maladaptative LVH including reduced compliance of the heart (93) and also contributes together with the reduced capillary density, to oxygen starvation that increases the susceptibility to ischaemia (85, 89). Another detrimental consequence of fibrosis, together with electrolyte alterations seen in CKD, is the increased risk of arrhythmia (94).

2.4 Vascular Calcification in Patients with CKD

The three most common CVD presentations in CKD population are CAD, LVH and peripheral vascular disease. The main lesions responsible for the clinical manifestations in the coronary tree and peripheral vascular disease are atherosclerosis of the intima and vascular calcifications of the media (95). Medial vascular calcifications can involve the whole vascular system and they are particularly common in CKD (95). Normally mesenchymal stem cells can differentiate to adipocytes, osteoblasts, chondrocytes and vascular smooth muscle cells (VSMC). In the presence of CKD, aging, diabetes, inflammation and other toxins, the VSMC can differentiate to osteo/chondrocytic-like cells that can become calcified in a process similar to bone formation and results in vascular calcifications (96). This process is accelerated in the context of high calcium and phosphorus levels and abnormal bone remodelling.

Metabolic bone disease is a frequent complication in CKD and alterations in the control mechanisms for calcium and phosphorus homeostasis can occur in early stages of CKD and progress as kidney function decreases (97). There are two main abnormalities in bone metabolism:

1) High turnover: this is the result of hyperparathyroidism. It is well known that even in the early stages of CKD there is some degree of hyperplasia of the parathyroid glands and high levels of PTH (98, 99). Numerous factors can lead to this including the retention of phosphorus, the decrease in the levels

of calcitriol, increase PTH secretion, increase parathyroid growth, skeletal resistance to the actions of PTH, and hypocalcaemia. All of these factors are closely interrelated and one or more can be predominant in a particular stage of CKD (97).

2) Adynamic bone: also known as low-turnover bone disease, is more common in dialysis patients. It is characterised by a slow rate of bone formation - its pathogenesis is not well defined, but it seems multifactorial (100).

This condition may result from a hypoparathyroid state that is due to the use of high-dialysate calcium concentrations, administration of high calcium loads from calcium-containing phosphate binders or and the use of vitamin D sterols (97).

High turnover and adynamic bone are different skeletal abnormalities and generate a wide spectrum of skeletal changes that can result in a variety of mixed patterns known as “mixed renal osteodystrophy” with results of the effects of hyperparathyroidism together with mineralisation defects (97).

Other factors that may lead to decreased bone formation are age, increased peptides in the circulation (such as osteoprotegerin and N-terminally truncated PTH fragments), uraemic toxins, reduced expression of PTH receptors, alterations in concentrations of growth factors and cytokines that affect bone turnover, acidosis, corticosteroid therapy–induced osteoporosis, or malnutrition (97).

Both high and low bone turnover play a role in the formation of the vascular calcification either by not allowing calcium and phosphorous into the bone (low turnover) or by reabsorbing the calcium out of the bone (high turnover)(96).

Lack of inhibitors/regulators of calcifications can also play a role in the development of vascular calcifications in this population (Figure 2) (96).

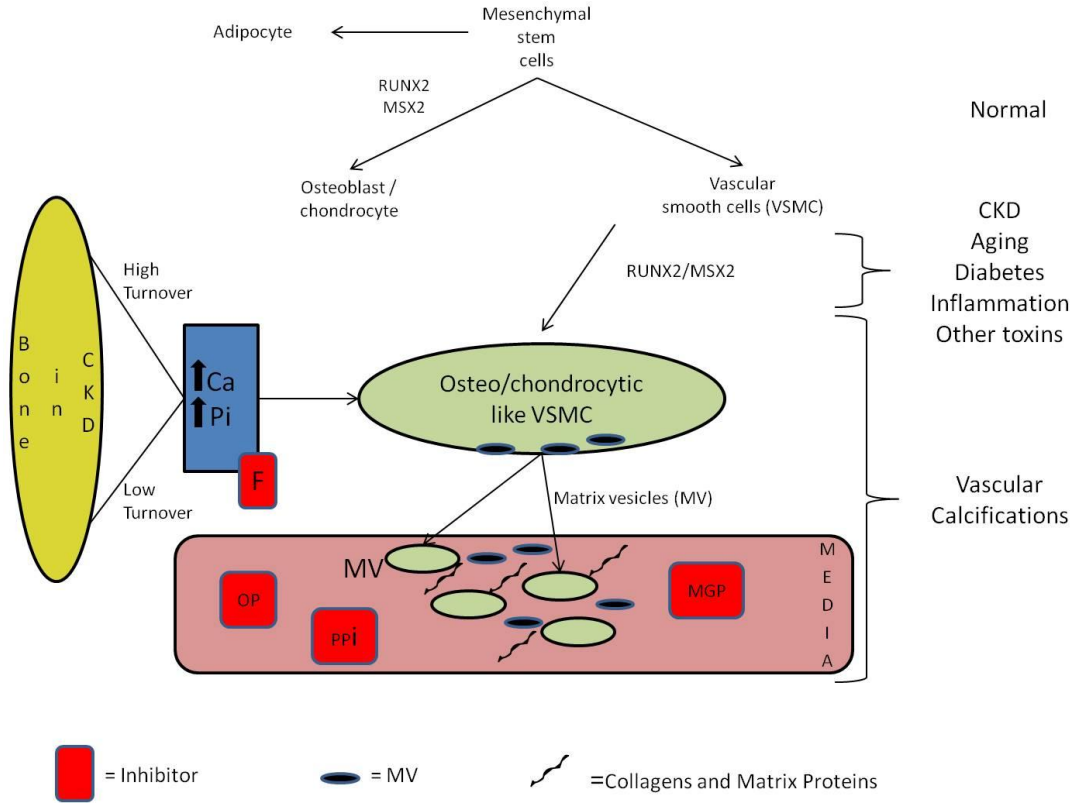

Figure 2: Pathogenesis of vascular calcifications. Adapted from (96). Mesenchymal stem cells in the setting of CKD, diabetes, aging, inflammation and multiple other toxins can differentiate into osteo/chondrocytic-luke cells (due to upregulation of transcription factors like RUNX-2 and MSX2), calcifie and lay down non-collagenous proteins as well as collagen in the intima and media and incorporate phosphorus and calcium into matrix vesicles to trigger mineralisation. The overall positive balance of calcium and phosphorus supports the generation of matrix vesicles and the cellular transformation. The extremes of bone turnover in CKD will also increase the availability of phosphorous and calcium. In the end the strength of the army of inhibitors (I) will influence whether an artery will calcify or not. Inhibitors are in the arteries (PPI=pyrophosphate, OP=osteopontine,MGP=matrix Gla protein) or they stand in the circulation (fetuin-A)

Several circulating biomarkers are involved in the regulation of the calcification process, such as the fibroblast growth factor 23 (FGF23), osteoprotegerin (OPG), RANK ligand, osteopontin (OPN), Klotho protein and bone morphogenetic protein-7 (BMP-7) (101).

Calcifications of the intimal and medial layers of the vessel wall are associated with cardiovascular symptoms, morbidity and mortality (96). In the CKD population, in the medial layer of the arterial wall calcifications develop mainly as a result of diabetes and mineral metabolism abnormalities, such as uraemia (96, 102). In the intimal layer, calcifications seem associated with a mix of atherosclerotic risk factors and renal impairment, showing an

association with kidney function abnormalities, smoking, diabetes, alteration of calcium-phosphorus metabolism and aging (102).

Nakamura et al (102) performed autopsy on 117 subjects with significant CAD and a wide range of renal function (ranging from normal to stage 5 of CKD). Most of adult patients with CKD suffer from both intimal and medial calcifications (102), whereas subjects with normal renal function only presented intimal calcifications.

Medial calcifications contribute to vascular stiffness, which increases the pulse-wave velocity and decreases diastolic blood pressure and increases systolic blood pressure (103). Medial calcifications contribute to the overall cardiovascular mortality in the ESRD population but they are not a marker of atherosclerosis (104).

Intimal calcifications, on the other hand, are more closely linked to atherosclerosis (104) and appear to be associated with cardiovascular events (103), in fact both ESRD and non-ESRD populations with predominantly intimal calcifications have a higher risk of mortality (104, 105).

ESRD worsens all the risk factors that contribute to the formation of both types of coronary artery calcification. Coronary calcification progresses during dialysis, with systemic inflammation acting as an important independent risk factor favouring progression (106, 107).

However, kidney transplantation can slow down - but is unlikely to stop – the progression of coronary artery calcification compared to the pattern observed in the dialysis population, possibly because of a regression in the uraemic milieu obtained after transplantation (95).

The progression of coronary calcifications after renal transplantation is strongly related to the baseline CAC score. The higher the baseline CAC score the more progression there is (95, 108). There is a variable association of other risk factors, particularly Framingham risk factors (smoking, blood pressure and dyslipidaemia) that can affect this progression (95).

The role of diabetes as a predictor for CAC is well known (109, 110) but its independent association with both kinds of calcification progression is still unclear (95).

The role of immunosuppressive therapy in slowing down the progression of vascular calcifications has been reported, but its mechanism is not completely understood (109, 111, 112).

Some patients, despite the presence of multiple risk factors, do not develop CAC even in long-term dialysis (113, 114). There is no clear explanation for this but the vast majority of authors who have examined this aspect hypothesised that these patients have high levels of protective factors either in the blood vessel or in the circulation or both (96). For example, the Fetuin-A serum level is responsible for 50% of the calcification inhibitory capacity (95). Levels of this inhibitor go down during inflammation, and low levels of Fetuin-A in dialysis are associated with vascular as well as valvular calcification and death (115).
In a large group of > 300 dialysis patients it was found that low concentration of serum fetuin-A levels was associated with significantly increased all-cause and cardiovascular mortality (116). The variability in the levels of fetuin-A has a possible genetic explanation, in fact Stenvinkel et al (117) discovered that a specific fetuin-A gene polymorphism (Thr256Ser) predicted particularly low fetuin-A levels and this was associated with an adverse prognosis compared to patients carrying alternative gene polymorphisms.

Calcifications can be detected through imaging techniques such as plain radiography and computed tomography (CT), the latter being widely used in clinical practice for the detection of CAC (CAC score). The CAC score is a marker of the amount of coronary calcification, but due to limitations in spatial resolution, cannot differentiate medial from intimal calcifications.

2.5. Guidelines for Cardiovascular Screening in ESRD

Cardiovascular screening is generally recommended in patients with ESRD under consideration for renal transplantation (66). Clinical recommendations are available provided by four main guidance documents (3-6, 118) The four main guidelines are shown in figure 3a and 3b.

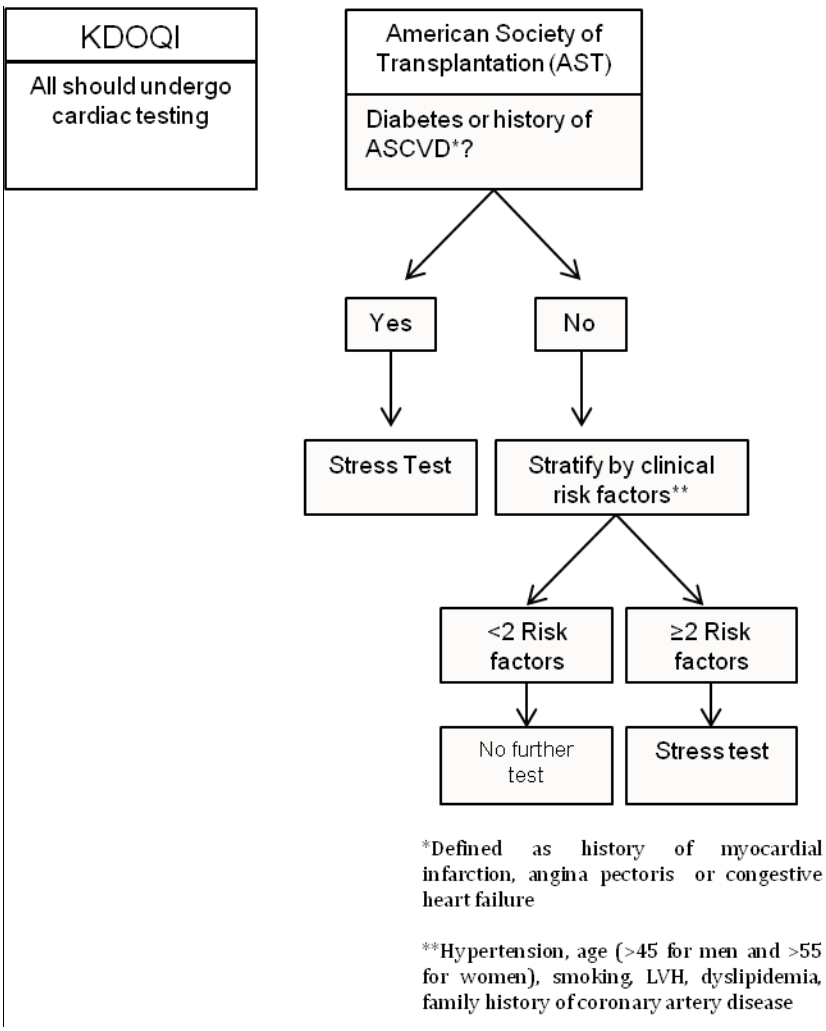

Figure 3a adapted from (119). KDOQI : Kidney Disease Outcomes Quality Initiative. ASCVD: arteriosclerotic cardiovascular disease

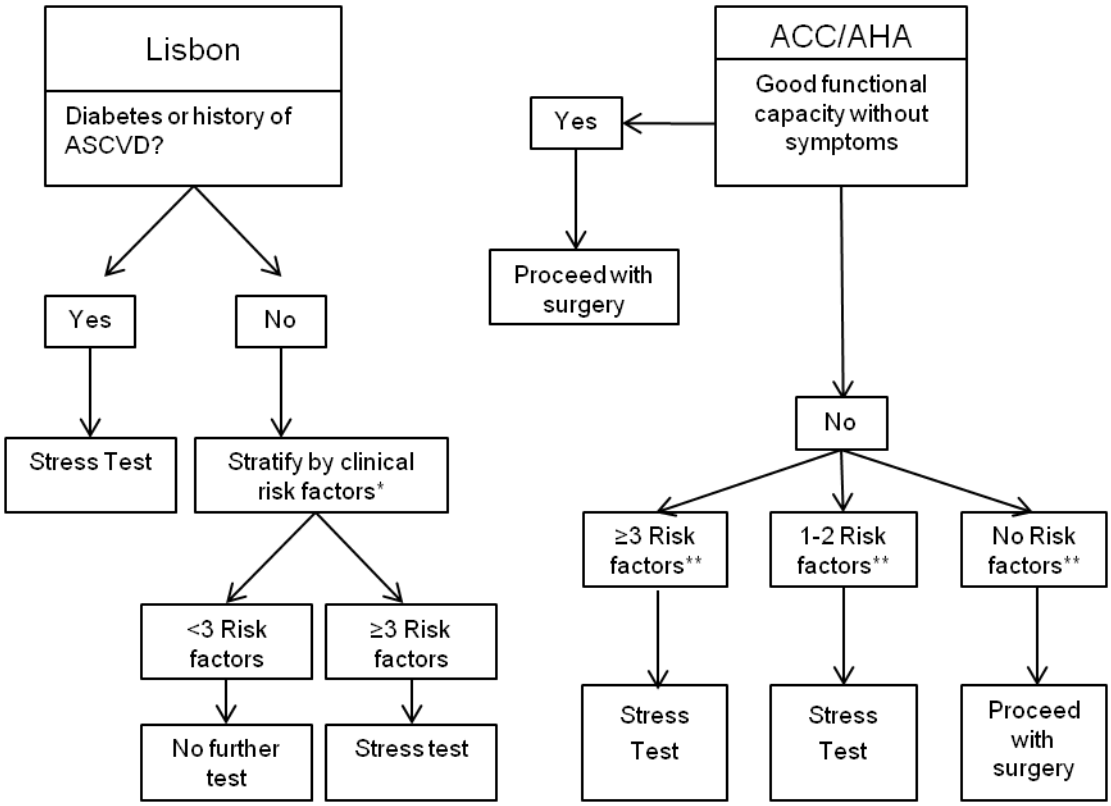

Figure 3b adapted from (119). ASCVD: arteriosclerotic cardiovascular disease; ACC/AHA: College of Cardiology/American Heart Association; MET: Metabolic Equivalent.

2.5.1 Kidney Disease Outcomes Quality Initiative (KDOQI)

According to the KDOQI guidance (3), non invasive stress testing should be performed. This may include exercise treadmill testing, if patients are able to exercise, or a pharmacological stress test, e.g. dobutamine stress echocardiographycardiography or adenosine/dipyridamole stress myocardial perfusion imaging, based on availability and expertise.

Non invasive stress testing is recommended for:

- All patients with diabetes (to be repeated every 12 months)
- All patients with prior CAD:
  a) If not revascularised, to be repeated every 12 months
  b) If revascularised with prior percutaneous coronary intervention (PCI), to be repeated every 12 months

c) If revascularised with prior coronary artery bypass grafting (CABG), repeat after first 3 years and then every 12 months

- To be repeated every 24 months in high risk non-diabetic patients defined as:
  a) ≥ 2 traditional risk factors
  b) Known history of CAD
  c) LV Ejection Fraction ≤40%
  d) Peripheral vascular disease

2.5.2 Evaluation of Renal Transplant Candidates by the American Society of Transplantation (AST)

According to the Evaluation of Renal Transplant Candidates, published by the American Society of Transplantation (AST) (66), non-invasive stress testing is recommended in patients with:

- Diabetes mellitus
- Prior history of CVD
- ≥ 2 of the following risk factors:
  a) Family history of CAD
  b) LVH
  c) Age >45 years for men and >55 years for women
  d) Smoking
  e) Hypertension
  f) Dyslipidaemia

2.5.3 Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient (Lisbon)

According to the Lisbon guidance (5), non-invasive and/or invasive test should be considered in patients with the following conditions:

- Diabetes mellitus
- Prior history of CVD
- Multiple risk factors (does not specify the number of risk factors to justify a test):

a) > 1 year of dialysis
b) LVH
c) Age 60 years or older
d) Smoking
e) Hypertension
f) Dyslipidaemia

2.5.4 American College of Cardiology/American Heart Association 2007 Guidelines on Peri-operative Cardiovascular Evaluation and Care for Non-cardiac Surgery (ACC/AHA)

According to the ACC/AHA 2007 guidance (6), the decision to proceed with screening should be based on the symptoms and the functional capacity of the patient, known as Metabolic Equivalent (MET). The MET is a largely used physiological concept that expresses the energy cost of physical activities as a multiple of the resting metabolic rate (Table 1) (120):

- No test is recommended if the functional status is ≥ 4 METS
- If the functional status is ≤ 4 METS or unknown a non-invasive stress test is recommended, based on the following risk factors:
  a) Known ischaemic heart disease
  b) Compensated or prior heart failure
  c) Diabetes mellitus
  d) Renal failure
  e) Cerebrovascular disease

Recommendations for testing are stronger if there are ≥ 3 risk factors, but testing may be considered as well in patients with 1-2-risk factors.

Table 1: Metabolic Equivalent (MET) for different activities. Adapted from (121).

Physical activity	MET
Light intensity activities	**< 3**
Sleeping	0.9
Watching television	1.0
Writing, desk work, typing	1.8
Walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
Walking, 2.5 mph (4 km/h)	2.9
Moderate intensity activities	**3 to 6**
Bicycling, stationary, 50 watts, very light effort	3.0
Walking 3.0 mph (4.8 km/h)	3.3
Calisthenics, home exercise, light or moderate effort, general	3.5
Walking 3.4 mph (5.5 km/h)	3.6
Bicycling, <10 mph (16 km/h), leisure, to work or for pleasure	4.0
Bicycling, stationary, 100 watts, light effort	5.5
Sexual activity	5.8
Vigorous intensity activities	**> 6**
Jogging, general	7.0
Calisthenics (e.g. pushups, situps, pullups, jumping jacks), heavy, vigorous effort	8.0
Running jogging, in place	8.0
Rope jumping	10.0

2.5.5 Variability in Guidelines for Cardiovascular Screening before Renal Transplant and Ethical Debate

In a study published in 2011 by Friedman et al (119), the authors applied each guideline to a cohort of renal transplant candidate in order to identify variations between them. Data showed a large difference in the rate of cardiac evaluation form 100% (KDOQI) to 20% (ACC/AHA). AST and Lisbon respectively showed cardiac evaluation rates of 92% and 68%. These results showed that some guidelines (KDOQI, AST and Lisbon) had a more aggressive approach compared to a more conservative approach promoted

by the ACC/AHA, the latter recommending cardiac testing only in the presence of either symptoms or poor functional status.

In light of the operative and long term mortality, as well as donated organs being a precious and limited resource, there is an ethical debate on the impact and utility of cardiovascular screening in patients awaiting a transplant (7, 122-124). The rationale in favour of screening is that CAD is a major cause of premature CVD mortality. By identifying and treating early CAD there may be better chances that the outcomes of these patients may improve. However, there is at present little evidence to support cardioprotective therapy in this group. Uremic cardiomyopathy may be a stronger factor than CAD affecting CVD mortality in ESRD patients (125).

Although screening will identify patients with significant CAD, intervention is seldom performed (3% of cases) (7). The survival rate of patients who underwent intervention was reported as not significantly better than patients who were not treated, hence at present the benefits of intervention are not clear (122).

Another potential practical problem of screening may be its impact on the delay of the transplantation. Ideally, a screening process should be rapid. Patients on dialysis awaiting for transplant have a high mortality rate. Delays in wait listing may increase mortality even further. Future randomised controlled trials will be needed to clarify the impact of CAD and uremic cardiomyopathy on survival and cardiovascular event rates in asymptomic ESRD patients.

2.6 Invasive Coronary Angiography and Identification of Patients Requiring Coronary Revascularisation

In a study including 287 American centres, myocardial perfusion scintigraphy (MPS) was found to be the commonest first-line screening strategy in ESRD patients, while approximately 15% of centres used invasive coronary angiography as primary method (126).

Coronary angiography, the 'gold standard' for the assessment of CAD, is invasive and exposes patients to the risk of complications. Unpublished

statistics from the London Chest Hospital (2010-2012) showed that approximately 10% of ESRD patients undergoing angiography received coronary revascularisation. This figure is in keeping with the performance of the available guidelines whose positive predictive value in the identification of patients requiring coronary revascularisation is reported between 5.9% and 10% (119). Coronary angiography is a well established technique but it is riskier than non-invasive tests. Complications include arrhythmias, the risk of developing atrial fibrillation, thromboembolic events (which may result in stroke or myocardial infarction), haemorrhage at the site of vascular puncture, arterial thrombosis, and renal damage secondary to the use of intrarterial iodinated contrast. Importantly, coronary angiography in ESRD patients is riskier than in non-ESRD patients (crude 4-year survival: hazard ratio 4). Therefore, the current consensus us that the use of invasive angiography for merely diagnostic purpose should be minimised where possible (127).

2.7 Myocardial Perfusion Scintigraphy (MPS) in ESRD

MPS is a well-established, widely used technique in the general and CKD population. MPS enables the evaluation of cardiac perfusion and function at rest and during dynamic exercise or more commonly during pharmacologic stress. MPS requires the administration of a radioisotope (thallium-201 or 99mTc-Sestamibi) and a dedicated gamma-camera which is able to detect the gamma photons. The fundamental principle of the technique is the flow-dependent and/or metabolism-dependent selective uptake of a radioisotope tracer by functional myocardial tissue. Under stress condition, the abnormally perfused myocardium receives less blood flow than normally perfused myocardium. Stress images show the distribution of the radioisotope, and therefore the relative blood flow to the different regions of the myocardium. When comparing stress images with rest images it is possible to identify perfusion defects. These can be secondary to CAD or a consequence of uraemic cardiomyopathy. MPS does not require the administration of iodinated contrast. This is an advantage for CKD patients in pre-dialysis. Although the sensitivity of MPS for the detection of CAD

compared to invasive angiography was reported as >90% in non-ESRD patients, the majority of studies carried out in patients with ESRD reported lower sensitivity values in the range of 29-86% (2, 128, 129). The specificity of MPS in ESRD has been reported in the range of 72-76% (2, 128, 129).
Several factors may account for this. ESRD patients have high levels of basal adenosine and high resting coronary flow. Pharmacologic MPS generally uses adenosine or dipyridamole as vasodilator to induce stress by challenging the coronary flow reserve. Coronary flow reserve can be defined as the ability of the coronary flow to increase above the normal resting values when metabolic requirements demand it, and this is achieved mainly by dilatation and recruitment of small intramural coronary arteries (130). The higher resting blood flow may blunt the flow reserve, potentially compromising the sensitivity of MPS by decreasing the heterogeneity of radioisotope uptake, which is the basis of detection of CAD by this modality (129). Moreover, MPS can yield positive findings in case of LVH even when CAD is absent (131, 132). Although MPS perfusion defects are useful in identifying patients with an increased risk of future cardiovascular events (133), it is not clear whether the increased risk is due to CAD or other expressions of cardiac disease e.g., uraemic cardiomyopathy characterised by decreased myocardial cellular components, more fibrosis and LVH.

Recently, it has been reported (134) that MPS can perform well in a limited subgroup of ESRD patients, i.e. those who do not have cardiac symptoms and do not present any factor that can impact on the coronary flow, such as anaemia, family history of CAD or known CVD, hepatitis C virus infection, obesity (body mass index ≥30 kg/m2), autoimmune disease, hyperphosphataemia, abnormal calcium-phosphorus product and echocardiographycardiographically-established LVH. With characteristics such as LVH or some of the cardiovascular risk factors being rather common features (given the suboptimal performance of MPS in the majority of ESRD patients who present at least one or a few of these features) an alternative non-invasive strategy for diagnostic testing in these patients could be desirable.

2.8 Role of Dobutamine Stress Echocardiography and Cardiac Magnetic Resonance in ESRD

Dobutamine or dipyridamole stress echocardiography (DSE) detects inducible myocardial ischemia by detecting wall motion abnormalities under stress, which reflect underlying significant CAD. A large metanalysis (135) has recently shown that the prognostic value of an abnormal DSE is similar to that of coronary angiography in predicting outcomes of cardiovascular mortality and major acute cardiovascular events (MACE). The authors however found a moderate sensitivity of 80% in detecting inducible myocardial ischemia in patients awaiting transplant (135). There are several possible explanation for this. A reduced response to the stressor or presence of LVH can make the detection of wall motion abnormalities more difficult in ESRD patients (136). On the other hand, a negative stress echocardiography remains associated with low incidence of MACE (137).

Cardiac magnetic resonance (CMR) with gadolinium is contraindicated when the eGFR is below 30 ml/min/1.75 m2 due to the reported small risk of nephrogenic systemic fibrosis. Gadolinium free techniques, however, are safe and could play a role in this population. In the general population, dobutamine CMR has excellent diagnostic accuracy for detection of significant CAD (138) as well as an excellent prognostic utility in patients with known or suspected CAD (139) . Very little data however are available in the ESRD population.

It has been shown recently that CMR can play a role in LV myocardial tissue characterization using the native T1 mapping technique (140). This magnetic resonance imaging technique is sensitive to the difference in the native longitudinal relaxation time (T1) of tissues, therefore it can be applied without the injection of gadolinium. Tissue changes characterized by an expansion of the myocardial extracellular volume compartment will have an

abnormal T1. These changes can be detected and quantified. It was found that hemodialysis patients may have prolonged T1 relaxation times, which,correlated with increased LVH and may suggest increased diffuse myocardial fibrosis.

Diffuse myocardial fibrosis detected with imaging could be used as a prognostic marker and to target specific treatments. Deep tissue phenotyping with this non-invasive approach could reveal useful to opmitise the timing of renal transplantation to maximize cardiovascular outcomes.

Chapter 3: Coronary Artery Calcium (CAC) Score

3.1 Technical Aspects

The detection of coronary artery calcifications with electron beam computed tomography (EBCT) and computed tomography (CT) provides a fast method for the assessment of coronary artery calcification with no need of contrast media injection (141).

At present, EBCT scanners are no longer in production having been superseded by CT scanners.

CT can detect calcifications in the vessel walls because of their X-ray attenuation which is higher than those of the myocardium and epicardial tissue, and similar to that of bone (142). In the heart, motion-free images are essential in order to have accurate quantification of calcification in the coronary arteries. For this reason, electrocardiographically (ECG)-synchronised protocols are used for image acquisition. Generally, 3mm-thick images are reconstructed over the heart range, with a slice interval of 1.5mm. The effective radiation dose associated a CAC score scan varies greatly from 0.8 to 10.5 mSv (with a mean of 2.3 mSv) across CT scanners of different generations, primarily depending on the use of different acquisition protocols. With current technology, CAC score scans are associated with radiation exposures of the order of 1-3mSv. CAC score scans can be acquired using either retrospectively-ECG gated protocols (as in older generation scanners) which are associated with higher radiation exposures, or prospectively-ECG triggered protocols (new generation scanners), generally associated with lower radiation exposures (143). Briefly, in prospectively ECG-triggered protocols ('step-and-shoot' scanning) the table moves in a step-wise fashion and X-rays are generated only when the table is stationary. In retrospectively ECG-gated protocols (helical or spiral scanning), there is a continuous emission of X-rays while the table moves through the scanner gantry, which explains the higher exposure associated with this protocol. An in-depth discussion of the available scan protocols for cardiac CT is reported in chapter 4.1.

For this study we used a modified prospectively ECG-triggered protocol available on our second-generation dual-source CT scanner, i.e. a prospectively ECG-triggered high-pitch spiral acquisition protocol (Flash mode, Siemens, Forchheim, Germany). In this protocol, table movement and X-ray emission were prospectively synchronised with a phase starting at 60% of the R-R interval. Table movement had a speed of 45cm/s, allowing for reduction in patient radiation exposure. Previous studies have reported consistency and good reproducibility of this method when compared to traditional scan protocols(144).

3.2 The Agatston CAC Score

The Agatston CAC score was developed by Arthur Agatston and colleagues (145) in the 1980s, when multiple large-scale studies for the detection of coronary artery calcium using a dedicated EBCT scanner were published. This technique relies on some assumptions:

- Any structure with a density of 130 Hounsfield units (HU) or more, and having an area of 1mm^2 or more, was considered a calcified focus.
- The foci overlying the coronary arteries were considered calcified plaques.
- A minimum area of 2 to 4 pixel was considered for measurement, with one-pixel foci considered as noise.

To obtain the Agatston score, the area of a calcified lesion on a 3-mm slice is multiplied by a density score factor from 1 to 4, which depends on the voxel with the highest attenuation contained in that focus.
Density scores 1,2,3 and 4 represent the densities 130-199 HU, 200-299 HU, 300-399 HU and ≥ 400 HU, respectively.

By adding up the scores for the calcified lesions in the coronary arteries the total Agatston CAC score is obtained.

Ranges of Agatston CAC score were used to define four categories associated with increasing risk of significant angiographic CAD (≥50% diameter stenosis) (Table 2)(146).

Table 2: Agatston CAC score categories for general population

CAC (Agatston)	Risk	Description
0	Non-identified	Minimal risk of having a cardiovascular event in 5 years.
1-10	Minimal	Low risk of having a cardiovascular event in 5 years.
11-100	Mild	Mild risk of having CAD exists.
101-400	Moderate	Moderate risk of having CAD exists.
>400	Severe	There is a significant risk of having cardiovascular events within the next 5 years.

CAD = coronary artery disease;

3.3 Clinical Application of CAC Score

In the last few decades, the CAC score has become an established method for cardiovascular risk assessment. Its role for risk stratification, and its prognostic value are well known.

In the general population, coronary calcium is a marker of coronary atherosclerosis. Therefore, there is an association with cardiovascular events such as myocardial infarction, mostly related to the rupture of vulnerable plaques (147).

Although this non-contrast technique only allows the detection of the calcified component of atherosclerosis and non-calcified plaques cannot be identified, a good correlation has been found between CAC score and the total amount of coronary atherosclerosis detected by intravascular ultrasound and histology (148, 149). For this reason, despite the known tendency to underestimate total plaque burden, CAC score is considered a reliable

indicator of the total amount of coronary atherosclerosis (142). CAC score has also been found to be more closely associated with total coronary plaque burden than the presence of luminal stenosis (149). An increasing amount of calcium in the coronary arteries correlates with an increasing probability of having significant, angiographically proven coronary artery stenosis (149). On the other hand, the total CAC score refers to the entire coronary tree and cannot be used to diagnose site-specific coronary luminal stenosis (150).

3.3.1 Cardiovascular Risk Assessment

CAC score has a high sensitivity and negative predictive power for obstructive CAD and it has been extensively validated as marker for cardiovascular disease.

The association between CAC score and traditional Framingham Risk Score (FRS) has been evaluated. CAC score was shown to have independent incremental value in the prediction of events in an asymptomatic population (151, 152). In a large cohort of 10,377 asymptomatic individuals with cardiac risk factors, it has been shown (153) that not only that CAC score is an independent estimator of all cause mortality but also that the 5 year survival rate worsens as the CAC score increases from levels of ≤10 to greater than 1.000.

The CAC score helps in the reclassification of patients in more appropriate CAD risk categories. For instance, it was shown that intermediate risk patients with a high CAC score (>300) had a 28% 10 year rate of cardiac death that would reclassify them in the high-risk category (154).

3.3.2 CAC Score in Asymptomatic People

A recent meta-analysis involving more than 29,000 asymptomatic subjects showed that the annual event rate for those with a zero CAC score was only 0.12% (155). A negative CAC score was also found to be more predictive of decreased cardiovascular events when compared to a negative stress test or normal intima media thickness on carotid ultrasound (156, 157). Even in diabetic subjects with a negative CAC score the cardiovascular risk was similar to subjects without diabetes (158).

According to the 2010 ACCF/AHA practice guidelines (159), the measure of CAC score was considered appropriate for the assessment of cardiovascular risk in asymptomatic adults with low-intermediate risk (6-10% 10-year risk), intermediate risk (10-20% in 10-year risk) and diabetic patients.

In practice, a negative CAC score suggests that the presence of atherosclerotic plaque is unlikely. Conversely, the presence of coronary calcium in an asymptomatic subject does not provide a rationale for revascularisation, but it can identify subjects with preclinical atherosclerosis who might benefit from risk factor modifications, potentially medical treatment and/or further testing (160). Therefore, as a specific marker of atherosclerosis, CAC score has been consistently proven to be valuable for prognostication, discrimination, calibration and reclassification for cardiovascular disease in selected subjects (161). In general, however, the unselected use of CAC screening of the entire population is not recommended by current practice guidelines (162, 163).

3.3.3 CAC Score in Symptomatic Patients

The role of CAC score in patients with chest pain and suspicion of CAD has been shown in several studies, particularly its role as a gatekeeper for further testing (164). In particular, when a zero CAC score was used to identify patients without obstructive CAD, the test had a sensitivity of >95% and a negative predictive value (NPV) of 99% (164).

The UK-based National Institute for Health and Care Excellence (NICE) has supported the use of CAC score as a first line test for symptomatic patients with stable chest pain of recent onset and a low (<30%) pretest probability of CAD (165). It has also been suggested that CAC score may have a role in the management of patients with low-risk acute chest pain. Patients with negative troponin, no ECG changes and a zero CAC score could be discharged without further testing, in keeping with the 2010 UK NICE guidelines (164, 166). The American Heart Association scientific statement (167) reports that "a negative test (zero CAC score) makes the presence of atherosclerotic plaque, including unstable and vulnerable plaque, highly unlikely, and consistent with a low risk (0.1% per year) of cardiovascular events in the

next 2-5 years" (160). Although in the more recent UK NICE guidance published in 2016 (168) the use of CAC score has been superseded by CTCA due to the recongnised risk of underestimating non-calcified plaque by the CAC score, the added benefit patient associated with this approach cannot yet be established

3.4 CAC Score in ESRD

At present there are relatively few published data regarding CAC score in the ESRD population. It has been reported that CAC score was significantly associated with future cardiovascular events, cardiovascular death and all-cause death in patients on dialysis without cardiac-related symptoms (106, 113, 169, 170). It has also been shown that the severity of CAC score at the time of initiation of dialysis was a significant predictor of all cause mortality; in particular, a baseline CAC score >400 was associated with a greater than four-fold increase in mortality (113).

It is important to highlight that in this population a very high CAC score may be associated with cardiovascular death and all cause death, but this may not always imply the presence of underlying obstructive luminal CAD (171-174).

The progression of coronary calcifications also plays an important role in the mortality of this group of patients with relation to the treatment of hyperphosphatemia. Block at all (170) not only confirmed that the baseline CAC score was a significant predictor of mortality, but also demonstrated that phosphate binder choice and mineral metabolism were linked with mortality in hemodialysis patients. The choice of calcium phosphate binders as opposed to sevelamer in the treatment of hyperphosphatemia was associated with a doubling of mortality. Sevelamer is used to treat hyperphosphatemia and it is phosphate binding drug which prevents the absorption of phosphate(175). In the ESRD population coronary calcification can be present in both the medial muscular layer and in the subintimal layer of the vessel wall, but only intimal calcifications are a specific marker of atherosclerosis (104). Both types of calcification are captured when measuring the CAC score. Medial calcifications contribute to the overall calcification, indicate vascular damage secondary to uraemia, but are not associated with atherosclerosis (104). For this reason, it has been suggested

that the normal cut-off value of ≥400, indicative of an elevated atherosclerotic burden in the general population, may not apply to ESRD patients. At present there is no unequivocal data suggesting the best CAC score cut-off in this population to predict cardiovascular events and mortality.

A non-negligible proportion of ESRD patients can have zero CAC score (174), which makes significant CAD very unlikely. Similar to the pattern observed in non-ESRD patients, also in ESRD patients a baseline zero CAC score is associated with a significantly lower rate of cardiovascular events compared to patients with positive CAC score (CAC score >1) (113). In one study (169) no cardiovascular deaths were observed at a mean follow-up of 48.8 months in the group of ESRD patients with zero CAC score on chronic haemodialysis. Moreover no development of calcification has been noted in 18 months follow-up after dialysis initiation in one study, regardless of the choice of phosphate binders (170).

For these reasons, a zero CAC score can be considered a valuable practical diagnostic result in ESRD patients without cardiac symptoms. A zero CAC score implies that further testing for coronary atherosclerosis or CAD-related ischaemia could be avoided (169, 174).

3.5 Warranty Period of Zero CAC Score

Several studies have stated the favourable prognosis of zero CAC score in maximum 5 years follow-up (155, 176, 177). Importantly, a recent study examined a much longer-term prognostic utility of CAC score in a large cohort of asymptomatic individuals with cardiac risk factors and without known CAD (152). The authors performed a 15 year follow-up on 9,715 individuals (of whom 4,864 had zero CAC score) and showed that a zero CAC score was associated with a low risk of mortality (in both sex groups) for more than 15 years in subjects younger than 60 years of age, and for 14 years for subjects 60 years of age or older (low-risk and intermediate-risk groups). A zero CAC score was associated with a warranty period of 5-6 years for high risk patients. This period is longer compared to that of low-risk or

intermediate-risk patients with any measurable CAC score (CAC score >0) (152).

Chapter 4: Computed Tomography Coronary Angiography (CCTA)

4.1 Technical Aspects and Contemporary Technology

4.1.1 Computed Tomography Basics and Technique

Computed tomography allows the evaluation of the human body in transaxial sections, and unlike linear tomography, it is able to generate images which are not influenced by the neighbouring regions of the body. It was introduced in the 1970s and was originally called computed axial tomography (CAT scanning).

The basic components of a CT scanner are the x-Ray tube, collimator and the detector array, which are installed on a rotating gantry. The patient lies on a table which is moved longitudinally through the gantry aperture and usually the plane of the gantry rotation is perpendicular to the table's long axis. With that said, some scanners can tilt the gantry up to 30° in order to have images acquired at an angle of the body (main application is CT of the head)(178). The X-ray tube is parallel to the rotation axis of the scanner and produces the X-ray beam; the collimator is mounted on the X-ray tube and its main role is to try to limit the scatter radiation in order to have accurate images(178).

The detectors are situated opposite the X-ray tube and they capture the X-ray beam after its passage thought the patient's body. The signal measured by the detectors is the result of the weakening of the X-ray beam when it passes though the different body tissues. When the attenuated X-ray beam reaches the detectors, it hits a "scintillator" which will then convert the detected X-rays into light. The light will then be converted into electricity by photodiodes, and a converter produces digital data and transmits them to the computer for analysis. The computer then translates the measurements into individual section images(178).

Each bidimensional CT image is usually calculated on a 512x512 matrix of pixels, ie. bidimentional picture elements.. More correctly though, a cardiac CT dataset shuould be described as an imaging volume made up of voxels, ie. three-dimensional picture elements that have a depth equal to the slice thickness(179). The multiple projections obtained by the rotation of the

gantry provide the attenuation values of the voxel and these attenuation values are assigned to the pixel that forms the image(179). As a general rule, the more projections obtained, the better the image quality. For image reconstruction, complex mathematical algorithms are required. The vast majority of the algorithms are based on the back-projection method. In this algorithm, the overall X-ray attenuation of a projection is assigned to each voxel along the X-ray beam and then the value of the voxel results from the sum of the values of all the projections along the X-ray coming thorough the voxel. The downside of this method is that images are blurred. In order to compensate for this and obtain better image quality, a convolution kernel is used before back-projection (this method is called filtered backprojection-FBP)(180). A convolution kernel is a filter that will adjust the value of a voxel according to the value of the adjacent voxels.

Although modern FBP methods are capable of quick reconstructions, they have several limitations. Image noise, poor contrast resolution and streak artefacts are limitations of FBP (180). This is mainly due to variations in the photons across the imaging plane, which ultimately results into an inverse relationship between noise and radiation dose when FBP is used (180). Recently, the introduction of more sophisticated reconstruction algorithms called collectively iteractive reconstruction (IR) made it possible to lower patient's raadiation exposure without compromising image quality (refer to section 4.1.6)

The first types of CT scanners for clinical use were capable of axial scanning only. These systems worked using the step and shoot technique in which the gantry had to stop after each 360-degree rotation. The gantry could not rotate continuously around the patient as in spiral or helical scanning. The main reason for this was that the gantry received its electrical supply via hard wires.

A dramatic advantage was gained with the introduction of the slip ring technology. Following this development, the gantry could rotate continuously around the patient with the table translating without interruption. This

technique has been referred to as helical, volume, or spiral scanning. The main advantage of this technique was a significant increase in scan speed, which was increased even further with the introduction of the multislice or multidetector technology. The latter technology enabled scanning several slices per revolution thus including larger parts of the body in the scan in reduced time.

Several CT scanner generations can be described as follows.

First Generation: these scanners used the "translate and rotate movement" meaning that the tube and detector moved in a series of sweeps and rotations around the patient. The X-ray tube produced a pencil-like X-ray beam, which was detected by one single detector. The average scanning time for one slice was 5 minutes (181).

Second Generation: this generation of scanners were still using a translate-rotate motion but they were equipped with multiple detectors and the X-ray beam was fan shaped. This allowed to cover a larger area and the scan time was reduced to roughly 90 seconds per slice (181) .

Third Generation: the main advantage was achieved by the use of a pure rotational motion instead of the translate-rotate one. This was accomplished with a wide X-ray fan-beam which was able to cover the entire patient body, using multiple detectors to detect the X-ray beam. Detectors and X-ray were linked, and were able to rotate together around the patient. This resulted in a reduction of scanning time to 20 seconds per slice (178).

Fourth Generation: the main advantage was achieved by using an outer fixed detector array system, with the X-ray tube only rotating around the patient with the slip-ring technology. The scan time per slice was significantly shorter (1 slice per second) (181). This technology is however superseded in current CT technology.

Modern CT scanners are based on third generation configuration: a wide X-ray beam is detected by a multi-element detector array. Both the X-ray tube and detector array rotate around the patient.

Cardiac CT became possible with the first generation of multi-element CT scanners that were capable of cardiac synchronised acquisition. This was with 4-detector CT (1999). Cardiac CT was then more widely validated in patients with 16-detector CT scanners (2000-2003). Sixty-four detector CT (2004) showed improved robustness for clinical applications and is now considered the minimal technical requirement for performing cardiac CT.

With the dual-source technology there has been improvement in temporal resolution.. This technology uses two X-ray tubes and two detectors arranged at 90° angles instead of a one single X-ray tube (single source scanner). The two X-ray tubes and detectors rotate simultaneously reducing image acquisition to half of the time required with single source technology. This permits reconstruction of cross-sectional images at one quarter of the gantry rotation time (182). It has been shown that image quality is significantly better with dual source scanners when compared to single source scanners, even at higher heart rates. Three iterations of dual source CT scanners have been introduced so far, all by a single manufacturer (Siemens): the Somatom Definition (2006), the Somatom Definition FLASH (2009) which was used in this project, and more recently the Somatom FORCE (2015). Although some authors suggested that the use of beta-blockers may become unnecessary when using dual source CT technology (182), this issue is still debated and the majority of practitioner still enforce accurate heart rate control for cardiac CT even in the availability of a dual source CT scanner.

At present, invasive coronary angiography still remains the gold standard for CAD assessment because of its spatial and temporal resolution (refer to section 4.1.3), however, over the last decade there have been dramatic advances in both CT scanner and software technologies that have achieved adequate volume coverage, sub-millimeter spatial resolution, and heart-freezing temporal resolution which permit accurate depiction of both cardiac

structures and coronary arteries (183). While first reports on the safety of cardiac CT date to 1999 with 4-slice CT scanners (184), the technique was proven feasible using 16- and 64-slice technology (185). The general consensus in 2017 is that 64-slice CT technology represents the bare minimum technical requirement to provide a clinical service of cardiac CT.

4.1.2 ECG-synchronization and Scan Protocols

Coronary arteries are small and rapidly moving vessels and even at slow heart rates exhibit significant translational motion. The translational motion speed is up to 60mm/s for the right coronary artery and 20-40mm/s for the left anterior descending and circumflex arteries (186). ECG synchronisation is critical to minimise the motion artefacts and acquire data at the right period of the cardiac cycle. Beta-blockers administration before the scan is often needed and recommended to obtain a low heart rate preferably below 65 beats/minute.

Across different vendors, the most widely used ECG-synchronization protocols for CCTA include retrospective ECG-gating and prospective ECG-triggering:

The retrospective ECG-gating mode consists of a helical acquisition (patient/table continuously advanced during the gantry rotation) with the X-ray tube turned on throughout the cardiac cycle (Table 3 and Figure 5) (187). The X-ray tube current can be reduced in the phases of the cardiac cycle not used for reconstruction of high resolution images to limit the patient's radiation exposure, which is called ECG-dependent X-ray tube current modulation (see also section 4.1.6.)

The prospective ECG-triggering mode involves axial acquisition (the table intermittently advances) with the X-ray tube on only for a specific period of the cardiac cycle, usually the mid-diastole, or a wider window (usually 40-70% of the cardiac cycle) if the heart rate is not optimal (Table 3 and Figure 5) (183).

The high-pitch spiral CT protocol has been introduced in the latest generations of dual-source scanners. This protocol uses a very fast table

speed (45m/s) in order to image the whole heart in one heart beat (Table 3 and Figure 4) (183).

In scanners with very wide detector (e.g. 320 slices) one gantry rotation without translation of the table is sufficient to acquire a cardiac volume (volume scan).

Table 3: CCTA protocols. Adapted from (188)

Retrospective ECG-gating Protocol	
Advantages	Disadvantages
• All heart rates • All rhythms (also AF and multiple VES) • Both systolic and diastolic images • Free phase selection • Overlapping consecutive images • Functional analysis	• High dose (11-19 mSv)
Prospective ECG-triggered protocol	
Advantages	Disadvantages
• Low dose (1.5-4 mSv) • Regular and low heart rate	• Vulnerable for HR irregularity and variability • No functional analysis
High-pitch spiral CT protocol	
Advantages	Disadvantages
• Low dose (<1-2 mSv) • Relative low contrast material amount • Overlapping images • No stack artefacts	• Low HR (< 60bpm) required → if >65 bpm: β-blocking • Only diastolic images • Vulnerable for HR irregularity and variability • Only 33.2 cm FOV • Images along the Z-axis come from slightly different position in the R-R interval

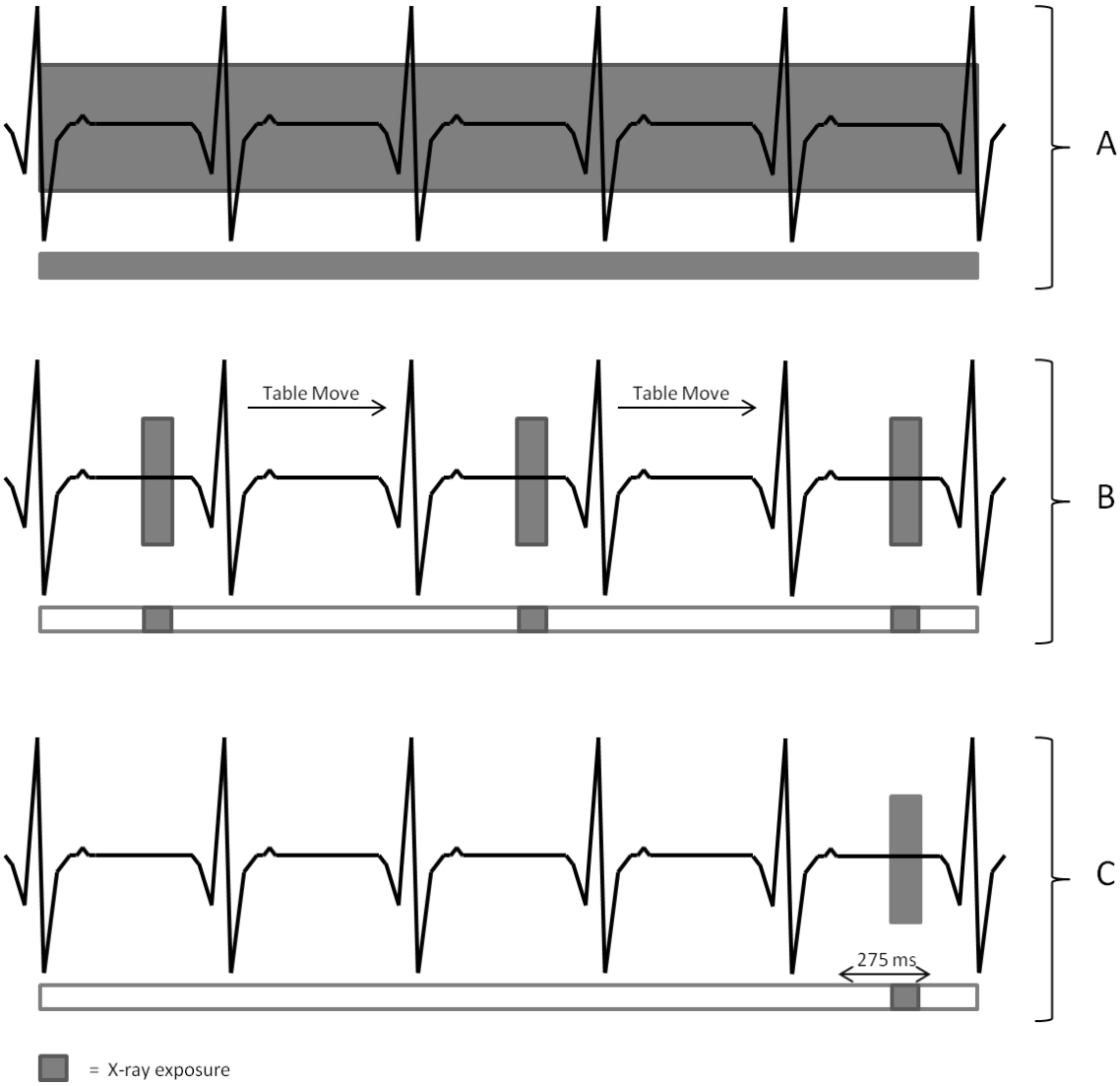

Figure 4: Schematic drawings of retrospective gating (A), prospective triggering (B) and high-pitch spiral(C) techniques. Adapted from (188)

4.1.3. Temporal Resolution and Spatial Resolution

Because of the small size of coronary arteries and their movement during the cardiac cycle a high spatial and temporal resolution are required in order to obtain adequate image quality (189).

Spatial resolution is defined as the minimum distance at which two signals can be identified as separate (190). Temporal resolution is the time it takes to acquire data for the reconstruction of one image (191).

4.1.4. Reconstruction and Post-processing

Data used for image reconstruction are obtained during the relative "motion-free" period of the cardiac cycle (mid-to-end diastole and end-systole) and this is usually obtained in stable heart rates (192).

Depending on the protocol used, reconstruction of consecutive datasets (usually every 5%-10%) of the cardiac cycle allows evaluation of the coronary arteries in different moments of the R-R interval. The evaluation of left ventricular systolic and diastolic volumes is also possible if the scan is being acquired using a retrospectively-gated spiral technique, or a wide prospectively-triggered technique, thus allowing the estimation of the left ventricular ejection fraction. A tailored reconstruction field of view (FOV) which includes the heart and the descending thoracic aorta is ideal for image evaluation, optimizing the utilization of the 512x512 pixel matrix.

The most reliable and widely used post-processing technique for image visualisation and analysis is multiplanar reconstruction (MPR), which allows to accurately visualise the whole coronary tree in multiple planes, including arbitrary planes, in order to assess the degree of luminal narrowing. Curved MPR's are also useful to visualise images of the coronary arteries along the vessels' centrelines.

4.1.5. Patient Selection and Preparation

Important contraindications to a CT scan may include pregnancy, known allergy to iodinated contrast and severely impaired renal function.

Even with new generation scanners, obtaining good quality images can be challenging. Artefacts can occur if patients are not adequately prepared and not compliant with the breathing instructions. It is recommended to fully explain the procedure to the patients in order to reduce anxiety, which in turn can have an impact on the heart rate. Artefacts are mainly caused by inability to cope with the breath-holding instructions during the scan, as well as fast and/or irregular heart rates. Patients should be able to perform an adequate breath-hold maneuver for as long as the expected scan time. Deep breaths should also be avoided as it may result in a Valsalva manoevre, which

can be the cause of low contrast attenuation in the coronary arteries due to "trapping" of the contrast bolus in the pulmonary circulation.
Sublingual nitroglycerin is given in order to dilate the coronary arteries and enhance confidence is coronary stenosis assessment, but disadvantages may include reflex tachycardia and severe headache in some patients.

4.1.6. Radiation Exposure

Radiation dose has become a growing concern with the increasing use of radiological testing and particularly CT. The radiation dose of CCTA can vary on the basis of the scanner generation/model, and the protocols used.
The most commonly used parameters to evaluate radiation dose are:
-Volume CT dose index (CTDIvol): this is an indicator of the scanner radiation output and its units are milligrays (mGy). This parameter does not provide information on the radiation dose to the patient (193).
-Dose-length product (DLP): describes the linear extent of the exposure to the patient and it is obtained by multiplying the CTDIvol times the centimeters of coverage. DLP units are mGy-cm(193) .
- Absorbed dose (patient dose): it describes the quantity of ionizing radiation deposited in tissue and it is expressed in milligrays (193).
- Effective dose takes into account the differing type and energy of the radiation source and also the biological harm from exposure to a particular organ (tissue weighting). The effective dose is primarily used to define the risk of a health detriment due to the stochastic effects of ionising radiation to a population, rather than the calculation of risk for a specific individual (194). The risk coefficients used in calculating effective dose were derived from a cohort that included both sexes and all ages and depended primarily on the excess risk observed in survivors of the Japanese atomic bombings. The values are a broad estimate of risk for an average adult hermaphrodite phantom, which is a fairly unrealistic description of the human body (195). Although the effective dose is not applicable to any single individual, it is an extremely useful parameter for comparing and optimising imaging procedures that use ionising radiation.

Multicentre studies carried out between 2005 and 2007 have reported a variation in CCTA effective dose ranging from 4mSv to 30mSv (196, 197).

In order to minimise the dose, several methods are available (183). These include:

1) Limitation of the scan range along the z-axis.

2) Tube current-time product (milliampere-second or mAs) is the product of the X-ray tube current and the CT scanner exposure time per rotation (in seconds). The increase of the mAs results in an increase of the radiation dose. All the scanners have the possibility to actively modulate the mAs during the scan in order to apply radiation efficiently. In practice, the scanner will produce lower radiation in regions of lower attenuation and apply higher radiation only for the higher attenuation regions(193). Moreover, every vendor gives the possibility to modulate radiation dose according to patient's size. We used this technique in our study which is called CareDose4D for Siemens.

3) Use of ECG-dependent current modulation to reduce the tube current in a specific part of the cardiac cycle.

4) Tube voltage (kV): indicates the peak energy of the X-ray photons beam in kilovolts. Lowering the kV will result in a radiation dose reduction as well as in greater contrast-to-noise ratio depiction of iodinate contrast in average-sized and small patients. The downside of a lower kV is an increased image noise, which can affect the quality of the images(193). Recently, dedicated software identify the most appropriate tube voltage according to patient's attenuation, for a given target contrast-to-noise ratio to be achieved in the CT images.

5) Prospectively ECG-triggered scanning protocol (refer to section 4.1.2).

6) Correct patient centering: it has been demonstrated (198) that miscentering the patients can result into an increase of the radiation dose. If the patient is too close to the tube, the scout or localizer will be larger and the automated tube current modulation system may incorrectly increase the mAs output.

6) Pitch: it is a parameter used in helical CT only. It is described as the ratio of table speed, in centimeters per 360° gantry rotation, to the total nominal

collimated x-ray beam width in the z direction. Given a constant output, as the pitch increases, the radiation dose proportionally decreases. In cardiac imaging the high pitch technique can significantly reduce the dose. The acquisition of the all heart can be achieved in one heartbeat with a smaller bolus of contrast (199).

7) Iterative Reconstruction is a novel approach used to decrease image noise without compromising on image quality for reduced-dose CT.

Image noise is determined in part by the range of mA used. Lowering the mA range translates into patient dose reduction at the expense of greater image noise. At lower current level iterative reconstruction can selectively reduce image noise by perforing multiple iterations of the reconstuction process (200). This is therefore a "statistical reconstruction" method which uses reiteration in the reconstruction process to remove noise.

4.2 Clinical Utility of Coronary Computed Tomography Angiography

4.2.1 Diagnostic performance

Diagnostic performance evaluates the ability of a qualitative or quantitative test to accurately classify individuals into categories (e.g. condition positive and negative)(201) and it can be appraised comparing the agreement between the outcome of the test and a reference standard for the condition.

Several studies have used coronary angiography as the reference to evaluate the diagnostic performance of CCTA in different patient groups (e.g. by age and gender) or different clinical scenarios (e.g. stable chest pain and acute chest pain) (185, 202, 203). These studies have focused mainly on sensitivity and specificity of CCTA.

Sensitivity is defined as the proportion of true positives correctly identified as such and it is obtained dividing the true positives by the sum of true positive and false negatives**.** The specificity is defined as the true negatives correctly identified as such and it is calculated dividing the true negatives by the sum of false positives and true negatives. (201). In order to interpret the results of a test it is also important to know the probability that a subject/patient is truly positive if a test is positive and truly negative if the

test is negative. The chance that this is the case is provided in the positive and negative predictive values of a test (201).

According to a recent systematic review, the sensitivity of CCTA in the detection of coronary artery stenosis compared to invasive angiography was ~98% (204). When sensitivity was examined according to age group, sensitivity remained largely unchanged (range: 95–99%). A greater degree of variability, however, was observed in the analysis of specificity. Specificity varied widely by age group ranging from 91% in studies with a mean patient age <59 years to 77% in studies with a mean patient age >62 years. A potential explanation is that CCTA may have lower specificity in the elderly due to higher levels of coronary artery calcification in older patients (205) leading to false positive findings, i.e. overestimation of stenosis severity.

It is well known that the presence of coronary calcification makes the assessment of the coronary arteries difficult. Kruk et al (206) investigated this aspect and found that:

- CCTA underestimates the coronary lumen area in presence of calcium. It was already known that calcium makes the evaluation of the lumen difficult resulting in a reduction of accuracy (207, 208) but the authors also found a correlation between lumen underestimation and smaller lumen (206). In summary, in smaller segments of the coronary arteries even artifacts caused by moderate calcifications may result into diagnostic errors (206).
- Although less common, CCTA can also overestimate the coronary lumen and the authors hypothesized that this may be due to the presence of small and less dense calcification which cannot be detected by CT (206). These findings found conformation in another study by van der Giessen et al. (209), where the authors found that upto 50% of the calcifications detected on intravascaulr ultrasound could not be seen on contrast enhanced CCTA because of their small size.

When compared to functional testing (stress SPECT, PET, echocardiographycardiography or CMR) CCTA was found to be the most accurate test to detect significant anatomical CAD (defined by invasive coronary angiography as >50% diameter reduction in the left main or >70% elsewhere or between 30% and 70% with a fractional flow reserve of ≤0.80) in a European population with stable chest pain and low prevalence of disease (210). It could be argued that this study used a hybrid, predominantly anatomical reference standard, so it was not surprising that CCTA as an anatomical test yielded closer results to the reference standard compared to the other imaging modalities included in this study.

A strong feature of CCTA, consistently confirmed across different studies, is its high negative predictive value (NPV) (167). CCTA has an excellent NPV (virtually 100%) in the exclusion of CAD (≥50% diameter reduction on angiography) (185, 211, 212).

CCTA however is an anatomical test performed in resting conditions and as such cannot provide information about the presence of stress-inducible ischaemia (213). Although CCTA can be used in clinical practice to rule in and rule out CAD, when CAD is detected the functional significance of coronary stenosis (ischaemia) cannot always be extrapolated based on coronary anatomy alone and in resting conditions. A further functional (stress) test may be required to guide patient management, particularly coronary revascularisation with either percutaneous coronary intervention (PCI) with stent placement, or surgical coronary artery bypass grafting (CABG) (214, 215).

In the FAME study (216) the relationship between anatomical coronary artery stenosis and its functional severity has been investigated by measuring the fractional flow reserve (FFR). FFR is a method used during invasive coronary angiography that uses sensor-tipped pressure wires to measure the maximal pressure in a coronary artery distal to a stenosis and in the ascending aorta. The ratio between these two pressure measurements is

used to establish the functional severity of a coronary stenosis, with functional significance defined by FFR <0.80.
The most important finding of this study was that one cannot rely just on the anatomy to identify ischaemia-producing lesions when assessing stenosis between 50-90%. Only in the presence of a coronary stenosis category >90%, visual assessment corresponds quite well to the lesion's capability of inducing myocardial ischaemia.

In a recent meta-analysis, Danad et al (217) investigated the diagnostic accuracy of different cardiac imaging methods in the assessment of hemodynamically significant CAD using fractional flow reserve (FFR) as reference standard (217). This study found that CMR was the most accurate test to identify hemodinamically significant CAD, while stress echocardiographycardiography and SPECT showed lower accuracy. Anatomical tests such as invasive coronary angiography and CCTA had low specificity (217). This was not surprising given the proven weak relationship between degree of luminal narrowing and ischaemia. The accuracy however improved when anatomical tests were followed by functional assessment, eg. with either stress echocardiographycardiograohy, SPECT or FFRct (see chapter 9) (217).

4.2.2 Prognostic Value

The extent and severity of anatomical CAD on CCTA correlates with the risk of cardiac events and death from cardiac cause (218-220). A recent meta-analysis pooled together the results of 18 prospective and retrospective cohort studies in patients with suspected or known CAD (n = 9592) (34). The pooled annualised event rate in patients with a normal CCTA was very low for major adverse cardiac events (MACE) (0.17%) as well as death/myocardial infarction (0.15%). The rates increased incrementally when stratified by none, non-obstructive (<50% coronary diameter reduction), and obstructive (>50% coronary diameter reduction) CAD (Figure 5) (34).

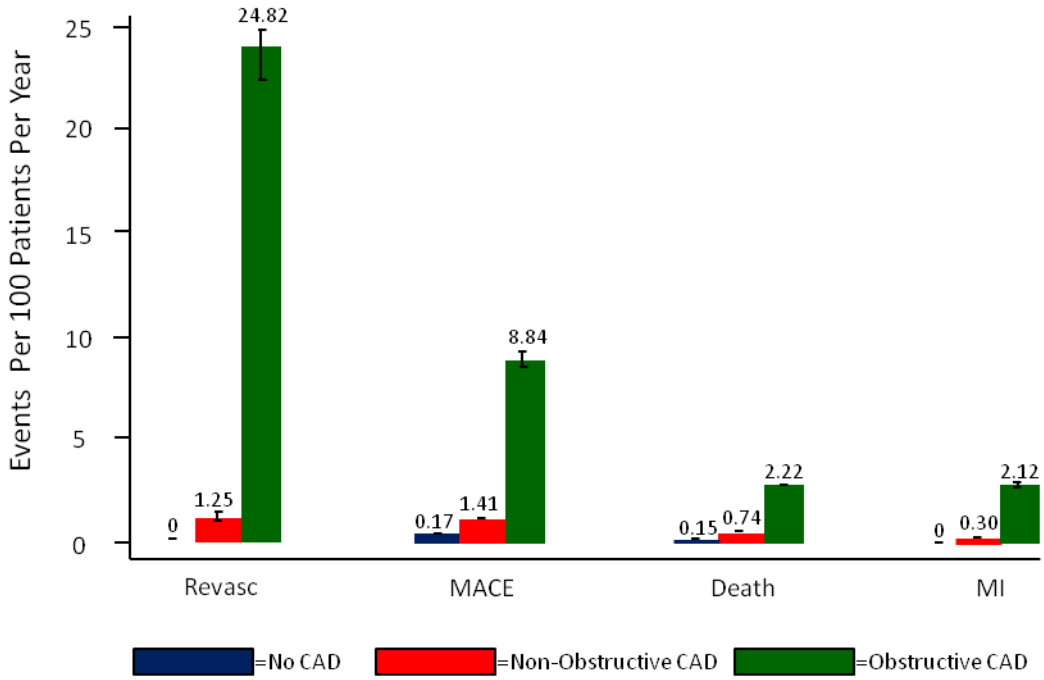

Figure 5. Percentage of annualised revascularisation (Revasc), event rates for combined major adverse cardiac events (MACE), death (all-cause)and myocardial infarction (MI),stratified by CCTA diagnosis of no coronary artery disease (CAD), non-obstructive CAD (<50% stenosis), and obstructive CAD (>50% stenosis). All groups were significantly different by analysis of variance ($p < 0.05$). Adapted from (221).

4.2.3 Clinical Decision Making

The role of CCTA to exclude obstructive CAD is nowadays widely recognised. However, there are limited data as to whether CCTA would also have the capability to differentiate high-risk patients who may benefit from revascularisation from patients who would be suitable for conservative management based on the CCTA findings.

This aspect was investigated by Min and colleagues (222) who studied retrospectively 15,223 patients without known CAD undergoing CCTA from the CONFIRM study. According to this study, the anatomical severity of CAD detected by CCTA predicted the clinical outcomes after revascularisation. In particular, the authors came to the following conclusions:

-revascularisation in subjects with high-risk CAD detected on CCTA (defined as a ≥50% luminal diameter narrowing in a major coronary artery) is

associated with a significantly lower rate of all-cause mortality (compared with medical therapy alone).

- subjects with lesser forms of CAD do not benefit from revascularisation.

It is, however, important to highlight that this was a retrospective non-randomised study and patients received treatment based on a mix of diagnostic tests, not solely based on CCTA. Importantly, there was no treatment adjudication based on the CCTA findings. For this reason, further randomised trials are necessary to confirm these findings (222, 223).

More recently Douglas et al in the PROMISE trial (224) studied a large symptomatic population in order to evaluate the better diagnostic strategy (anatomical versus functional testing) to assess CAD with death, myocardial infarction, hospitalisation for unstable angina or major procedural complication as a composite primary endpoint. As secondary endpoints they evaluated the radiation dose and the incidence of non-obstructive CAD detected on the coronary angiogram within the different strategies. The "anatomical" strategy using CCTA as first line test was not found to be associated with better clinical outcomes than the "functional" strategy and both strategies showed excellent midterm prognosis(224). CCTA strategy was associated with a lower incidence of non-obstructive CAD on the coronary angiogram, a 34% reduction in death and non-fatal MI at 12 months and with a reduction in radiation dose when compared with MPS (224). The study was not able to show the definitive superiority of the anatomical strategy versus the functional strategy, most likely due to short follow-up time (1 year) (225), but this was demonstrated in another large scale study named the SCOT-Heart (226).

In this randomised controlled trial the authors focused on the role of CCTA in patients with stable chest pain in order to assess the effect of CCTA on the diagnosis, management, and outcome. The results showed that adding CCTA to standard clinical care "markedly clarified diagnosis of angina due to coronary heart disease". Moreover, a reduction in further stress testing was observed, and patients could also benefit from more focused treatments which are apparently associated with reduction in fatal and non-fatal myocardial infarction. Although the authors observed an increase in

coronary angiographies in the vast majority of patients, the ICA showed obstructive coronary heart disease, including those with severe triple vessel disease . More recently Williams et al (227) in the SCOT-Heart trial demonstrated that the changes in diagnosis as result of CCTA findings resulted into more appropriate selection of patients for ICA and also resulted into better implementation of preventive therapies.

4.2.4 Cost-effectiveness

Cost-effective is anything effective and/or beneficial in relation to its cost. To assess whether a medical procedure or a test is cost-effective a comparison of its relative costs and outcomes against another test can be performed and this is defined as cost effectiveness analysis. The evidence regarding the cost-effectiveness of CCTA is limited.

A systematic review regarding the cost effectiveness of CCTA for coronary artery disease assessment was published in 2014 by Zeb et al (228). The authors analysed the literature from 2000 onwards and included randomised controlled trials, prospective and retrospective non-randomised comparative studies, decision analytic models, technology reports and case series which mentioned the cost-effectiveness, comparative effectiveness and downstream test utilisation associated with CCTA. The authors came to the following conclusions:

1) CCTA may be a cost-effective strategy (either as initial test or a secondary test to other modality) for initial evaluation of patients with 10-50% CAD prevalence in both near-term and long-term diagnostic periods.

2) For patients with CAD prevalence of >70% a strategy with initial invasive coronary angiography is more cost-effective but CCTA is still a cost-effective strategy when performed as a gatekeeper test before ICA in case of an equivocal stress test.

3) CCTA was also found to be cost-effective for evaluation of low-risk (defined as <30% CAD prevalence) patients presenting to the emergency department with acute chest pain.

More recently Genders et al (229) focused their analysis on the optimal image strategy for stable chest pain patients with intermediate probability of

CAD from the prospective of USA, UK and the Netherlands. The authors found that in USA and Netherlands the most cost-effective strategy would include CCTA as first line test followed by stress imaging test if at least 50% diameter stenosis is found in at least one coronary artery; invasive angiography would be the last test if revascularization is needed. In the UK, for men, the best strategy was full medical therapy if moderate narrowing (50-69% diameter reduction) was found on CCTA. For UK women the best strategy was stress echocardiographycardiography as first line test followed by invasive angiography if a stress echocardiographycardiography shows mild or moderate induced ischemia. Although some differences were found between the USA, UK and Netherlands, the authors concluded that CCTA was cost-effective as triage test for low-to-intermediate risk 60-years-old patients with non-acute chest pain.

4.3 Clinical Applications of CCTA

The 2013 ESC guidelines on the management of stable coronary artery disease (230) and the 2014 ESC/ European Association of Cardiothoracic Surgery (EACTS) guidelines on myocardial revascularisation (231) are recent European documents that focus on the role of CCTA as non-invasive test for CAD screening.

According to these documents the main clinical indications for CCTA are as follows :

Guideline 2013 European Society of Cardiology Guidelines on the Management of Stable Coronary Artery Disease(230) :

- Coronary CTA should be considered as an alternative to stress imaging techniques for ruling out stable CAD in patients within the lower range of intermediate pre-test probability (15-50%) for stable CAD in whom good image quality can be expected.
- Coronary CTA should be considered in patients within the lower range of intermediate pre-test probability (15-50%) for stable CAD after a non-conclusive exercise ECG or stress imaging test or who have contraindications to stress testing in order to avoid otherwise

necessary invasive coronary angiography if fully diagnostic image quality of coronary CTA can be expected.

- Coronary calcium detection by CT is not recommended to identify individuals with coronary artery stenosis.
- Coronary CTA is not recommended in patients with prior coronary revascularisation.
- Coronary CTA is not recommended as a screening test in asymptomatic individuals without clinical suspicion of CAD.

Guideline 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)(231):

- Coronary CTA is indicated to rule out CAD in symptomatic patients with intermediate pre-test probability (15-85%) for CAD.
- Coronary CTA is contraindicated to rule out CAD in asymptomatic patients.
- Coronary CTA is contraindicated to rule out CAD in symptomatic patients with high pre-test probability (>15% or >85%) for CAD.
- CT angiography should be considered before valve surgery in patients with severe valvular heart disease and low probability for CAD or in whom conventional coronary angiography is technically not feasible or of high risk.
- Electrocardiogram-triggered CT scans or epiaortic scanning of the ascending aorta should be considered in patients over 70 years of age and/or with signs of extensive generalised atherosclerosis

According to the UK NICE 2010 guidance for the evaluation of patients presenting with stable chest pain of recent onset (165, 232), CCTA was recommended for diagnosis and risk assessment of symptomatic patients with low-intermediate risk or pretest probability of CAD (10-29% estimated pre-test likelihood of CAD). This guideline was revised at the time of preparation of this thesis. The new NICE guidance update issued in 2016

(233) recommends CCTA as first line imaging test is patients with stable chest pain suspected for CAD regardless of the pre-test probability of disease estimated on clinical grounds.

Due to its extremely high negative predictive value (234) there is consensus that CCTA is considered appropriate as a first line test in individuals with symptoms, sex and age suggestive of low-to-intermediate pretest probability of CAD. A normal CCTA rules out presence of obstructive CAD and this applies to both patients with stable chest pain and those suspicious of ACS (183).

The use of CCTA in emergency departments has been evaluated in several studies and, in summary it was found that, similarly to the non-acute patients, a negative study is associated with an extremely low event rate (235).

From 2006 to 2012, observational studies (236-239) focused on the role of CCTA in the emergency department and all results were consistent with the ROMICAT I study(238) . The ROMICAT I showed that while a negative CCTA excludes ACS with high sensitivity (100%), acute coronary syndrome cannot be ruled-out in the presence of coronary plaques and this results in a reduction of the CCTA specificity (only half of patients with obstructive coronary disease defined as >50% diameter reduction on CTA, have acute coronary syndromes).

Several randomised effectiveness controlled trials (240-242) have explored safety and economic performance of cardiac CT in acute chest pain where CCTA was proven to be adverse event free (241) or having a low adverse event rate (240, 242). More importantly, examining the whole population of these three studies (> 3000 subjects), none of the patients were discharged with missed diagnosis of ACS. The same studies also highlighted how the CCTA, performed in acute chest pain, allows a rapid triage reducing unnecessary hospital admissions and reducing the time to discharge.

Moreover, the ROMICAT II trial authors (243) showed that high risk plaques detected on CCTA (positive remodelling, <30 HU, spotty calcium and napkin-ring sign which can be seen in a high risk plaque as a necrotic core covered

by a thin cap) in patients presenting at the emergency department with acute chest pain but without objective evidence (on initial ECG and troponin) of MI or myocardial ischaemia, improves the early diagnosis of acute coronary syndromes independently to the presence of significant CAD and clinical risk assessment. The suboptimal accuracy of CCTA in detecting ACS using the traditional criteria of significant stenosis may result in an increased number of downstream tests and interventions (243), but the accuracy can be improved by adding the high-risk plaque assessment. This area is a focus of intense research, and criteria for implementation of plaque analysis in daily clinical routine require definition, standardization and further validation.

Given CCTA provides a tri-dimensional dataset of the heart and coronary vessels, CCTA allows the assessment of the entire arterial wall, including the visualisation of the atherosclerotic plaque (244). This allows detection of CAD at early stages, assessment of total atherosclerotic plaque burden and plaque characterisation (244). It is well known that heart attacks may occur in a site of non-obstructive – but 'vulnerable' - plaque (245). In the context of CAD diagnosis and risk stratification, exercise testing or pharmacologic cardiac imaging (e.g. MPS) are sensitive to ischaemia secondary to high-grade coronary stenosis (160). For this reason, detection of preclinical coronary atherosclerosis may result in beneficial lifestyle modification, and may as well provide the rationale for initiation of preventive medical therapy.

At present however, there is limited evidence regarding the usefulness of CCTA in asymptomatic patients. For this reason, as well as the issue of radiation exposure and costs of imaging, CCTA is not recommended as a screening test in the general, unselected asymptomatic population (183, 246).

4.4 Limitations of CCTA

Several factors should be considered prior to referring a patient to CCTA in order to identify possible contraindications. Patients unable to cooperate with breathing instructions (who cannot hold breath for ~10 seconds) or

patients unable to lie down flat are unlikely to be imaged successfully with CCTA.

Contraindications to iodinated contrast use include prior/severe anaphylactic contrast reaction or renal insufficiency (but end-stage renal disease is not an absolute contraindication) for contrast induced nephropathy (refer to section 4.6) (247).

Contraindications for beta-blockers include severe chronic obstructive pulmonary disease, severe asthma, decompensated heart failure and advanced atrioventricular block.

Contraindications for sublingual nitroglycerin are severe aortic stenosis, hypertrophic cardiomyopathy and recent use of phosphodiesterase-5 inhibitor.

The presence of metallic pacemakers/intracardiac defibrillator leads, stents and mechanical prosthetic valves can produce beam-hardening and streaking artefacts over adjacent coronary arteries (183), however, these devices do not pose a contraindication to CCTA. High BMI (>40) can lead to decreased image quality unless scan parameters are optimised (X-ray tube kilovoltage, tube current, patient preparation and instructions, image reconstruction techniques), however, an elevated BMI however is not a contraindication to CCTA.

Motion artefacts can also occur particularly in patients with elevated heart rate and can result in degraded image quality. The presence of heavily calcified coronary plaques is one of the leading causes of misjudging lumen narrowing. This happens because calcifications can obscure the contrast-filled lumen, resulting most frequently in overestimation of stenosis degree (248). Adjusting the window level, using appropriate reconstruction kernels and post processing settings (e.g. thin-slice display) can help in visualising the lumen in calcified segments (249-251).

4.5 CCTA in ESRD

Limited data are available regarding the use of CCTA in the ESRD population (252-256). It has been reported that CCTA is feasible and safe to exclude major epicardial CAD in the asymptomatic ESRD disease population(252).

However, a further concern in the ESRD population is the contrast-related volume overload. Published data suggest that as a precaution it is safer to perform the CCTA as close as possible to the next dialysis session(253). More importantly, with a low amount of iodinated contrast volume (average 67ml), Jug and colleagues did not observe any significant volume overload in their study(253). In the study by Mao et al.(252), CCTA was very well tolerated and there was no increased 30-day adverse event rate including death, MI, congestive heart failure or any other reaction that can be attributed to the CCTA procedure.

CCTA in combination with CAC score has been found to be very useful in predicting cardiovascular events in the ESRD population. Patients with presence of both coronary artery calcifications and coronary artery stenosis detected on the CCTA had a higher risk of cardiovascular complications compared to those without any of them(253).

In the studies by Jug et al. and Park et al.(253, 254), CCTA showed a high diagnostic accuracy at per-patient and per-vessel level (using invasive coronary angiography as reference standard), suggesting that CCTA can be a reliable non-invasive imaging modality for guiding clinical management of ESRD patients. CCTA not only provided information about the coronary arteries but could also identify and quantify LV dysfunction (when retrospectively ECG-gated), which could be valuable additional information when trying to identify high-risk patients(253).

As in the normal population, high coronary calcium can affect the diagnostic accuracy of CCTA in this population(254). Surprisingly, however, in the few studies published, even in the presence of high calcium scores CCTA was very helpful in the exclusion of significant coronary artery disease(252, 253).

More recently Winther et al (256) analysed the diagnostic performance of CCTA in ESRD patients awaiting kidney transplant and they suggested that CCTA can play a key role in this population. All patients included in this study (n:138) underwent CCTA, MPS and invasive coronary angiogram and CCTA was found to have high sensitivity and NPV to diagnose coronary stenosis but not surprisingly it was associated with a high number of false-positive results (reduced specificity due to high coronary calcified plaque burden).

MPS sensitivity was found to be low (and this is in line with the already published data) and the authors suggested that this test could not be used as a first-line modality but it could have a role as a second-line test in presence of positive CCTA (especially in the presence of high calcium) by increasing the PPV and reducing the need for invasive coronary angiography - albeit at the cost of lower sensitivity.

Overall, the available data seem to suggest that CCTA can be considered a useful tool to rule out significant atherosclerotic CAD in the ESRD population, and it can be used as an initial diagnostic test to identify patients that do not need further testing (253, 254, 256)(Table 4).

Table 4: Diagnostic performance of CCTA in renal patients.

Year	Author	Reference Standard	Parameter	Sens (%)	Spec (%)	PPV (%)	NPV (%)
2015	Winther et al.(256)	ICA	Stenosis	93	63	41	97
2013	Jug et al.(253)	ICA	Stenosis	100	78	92	100
2011	Park et al.(254)	ICA	Stenosis	93	80	81	93

Sens: sensitivity. Spec: specificity. ICA: invasive coronary angiography. PPV: positive predictive value. NPV: negative predictive value. Stenosis parameter defined as >50% diameter reduction detected on CCTA.

4.6 Contrast Induced Nephropathy

Contrast-induced nephropathy (CIN) is an important complication of the use of iodinated contrast agent and it can be associated with an increased morbidity, including the need for short/long-term dialysis or renal transplantation (257).

Three components define CIN (258):

1) Absolute or relative increase in serum creatinine compared to the baseline values (increase of 25% or more, or an absolute increase of 0.5 mg/dl or more

in serum creatinine from baseline value, at 48–72 h following the exposure to iodinated contrast media).

2) Temporal relationship between the rise in serum creatinine and exposure to the iodinated contrast media. In particular, the first 24 h post-exposure are crucial in the development of CIN, in fact in 80% of patients who develop CIN, the serum creatinine rise was seen within the first 24 h post-exposure, and nearly all patients who developed serious renal failure had a rise in serum creatinine within this time frame (259).

3) Absence of other explanations for renal impairment (e.g. cholesterol embolism).

The risk of developing CIN is low in the normal population with preserved renal function (risk of 2%) but increases up to 12% to 27% in CKD population (260) and can go up to 50% in patients with concomitant CKD and diabetes (261).

Although most episodes of CIN are self-limiting and tend to resolve within 10 days (262), even a small persistent increased creatinine is associated with increased mortality (263). The risk of CIN can be significantly reduced by using a lower volume of contrast media (<100ml) with a potentially rewarding outcome. It is important to mention that patients on dialysis usually have some degree of residual renal function which contributes to the overall health and well-being of this population (264) and the use of iodinate contrast may compromise this.

Chapter 5: Nuclear Medicine and Echocardiography

5.1 Myocardial Perfusion Scintigraphy

Nuclear medicine uses radionuclides which have unstable nuclei (having an exceeding neutron) and decay until become stable. During this process there is emission of beta and gamma radiation which are used for nuclear imaging. The most commonly used radionuclide for MPS is technetium-99m. This atom has satisfactory gamma energy thus allows for good spatial resolution, has a short half-life (6h) and pure gamma emission. Technetium-99m (99mTc) is labeled with sestamibi or tetrofosmin for cardiac perfusion imaging (265).

The radiopharmaceutical is usually administered to the patient via intravenous injection and ideally it concentrates in the target organ; the gamma rays produced are detected by a gamma camera in order to produce an image, which results from the radionuclide distribution. The gamma camera has a multi-hole collimator, which has the role of reducing the background gamma radiation that can come from the patient but also from other sources in the room. After passing through the collimator, the gamma rays reach a large crystal (usually made of sodium iodide), which will absorb them generating a flash of light. The light is then absorbed by photomultipliers, which converts light into photoelectrons, which are then analyzed to produce images (265).

It is possible to study the dynamics of some organs; in particular, for heart function, separate images (of 40ms) are acquired at 20-30 different moments of the cardiac circle in order to image multiple moment of the cardiac circle. This allows calculation of the cardiac function and videos can also be generated (265).

The planar gamma cameras described above has the main limitation that it produces superimposed images. This can be addressed using the tomography technique with two methods: SPECT (single-photon emission computed tomography) and PET (positron emission tomography)(265).

SPECT imaging uses a gamma camera with a parallel hole collimator rotating around the patient who lies on a bed. With this technique several parallel

transverse image sections are imaged and also sagittal, coronal and oblique images can be generated as well as videos. Gating is also possible for cardiac studies in order to obtain information about cardiac function and perfusion (265).

One of the main problems of this technique is the attenuation of the photons within the body due to Compton scattering, which refers to the change in direction of the photons while they travel thought different body tissues and, as result, they are not detected by the gamma camera (266). As a consequence, reconstructed images would show a reduced activity in the centre of the source due to these missed counts. Using an algorithm for gamma attenuations when images are reconstructed solves this problem.

More recently, new and more advanced SPECT scanner have been developed which use semiconductors which, in response to gamma photons, combine the function of scintillation crystal and photomultiplier tubes by producing directly electron current. The vast majority of these scanners have a Cadmium-Zinc-Telluride (CZT) detector that operates at room temperature and has high-energy resolution and very high-count rate (267). This technology is called Solid state SPECT, enabling shorter imaging protocols with reduced injected doses of radio-isotopes and patient exposure (268).

5.2 Radiation Dose Reduction in MPS.

In the last decades there has been significant reduction in radiation dose for MPS. The main techniques used to reduce radiation dose are (269, 270):

-Radiotracer selection: radiation dose is directly related to the half-life of the radiotracer and dose of radiotracer administered. Usually 99mTc agents are more used than thallium 201 (201Tl) due to their shorter half-life, lower effective dose, and superior image quality. The radiotracer dose is also adjusted according to patien's BMI with a significant reduction in radiation dose which has been reported to be as much as 58% for patients and 50% for staff (271).

-Stress first or Stress-only technique: in this approach, the patient undergoes stress imaging first and if this is normal then there is no need for rest imaging. A stress test is considered normal when there is homogenous

myocardial perfusion, normal ejection fraction and normal left ventricle volumes during maximal stress and no ECG changes suggesting ischemia (272). If the rest scan is avoided the radiation exposure for the patient is 30% less and there is also a 40% dose reduction for the staff (273)

-Advantages in technology: significant technical progress has been made in recent years resulting into remarkable dose reduction. New iterative reconstruction methods with noise reduction and resolution recovery significantly increase image quality, allowing studies with half- and quarter-dose radiotracer protocols (274).

New solid-state SPECT scanners have significant increase in count sensitivity (275-277). These developments enable low-dose and ultra- low-dose MPS, with radiation doses which can be as low as 2mSv (270)

5.3 Positron Emission Tomography (PET) (178).

One of the commonest PET imaging radionuclides is 18-fluorine (^{18}F). This emits positive beta particles, which travel for approximately 2mm within the body before being annihilated by an electron. This produces two energetic photons, which are generated at the same time in almost opposite direction. PET technique is based on the detection and localization of these two photons. The PET scanner has a ring of detectors around the patient, which detects the photons to create images. Nowadays integrated PET-CT systems are used. CT and PET are mounted on the same support next to each other and once the CT images are acquired, PET images of the same section are subsequently collected. This technique allows almost perfect matching between the functional and anatomical images(178).

Cardiac PET has several applications and uses several tracers:

Fludeoxyglucose ^{18}F (18F-FDG) PET imaging is used for viability studies and it has been reported to have an average sensitivity and specificity around 90% for the detection of angiographically significant CAD and a very high accuracy for the prognosis of patients with suspected or known CAD (278).

PET myocardial perfusion imaging can be performed with different tracers such as oxygen-15 water, N-13 ammonia and 82-Rubidium. Myocardial uptake depends on the tracer extraction from the blood and the tracer

delivery and differences in the first-pass extraction influences the myocardial uptake in relation to the blood flow (279). The uptake can be passive (free diffusion) or can happen with active first pass extraction through the sodium–potassium exchange transporter (NA+/ K+ ATPase) (280).

Oxygen-15 water (O-15 H2O) has a linear uptake and free diffusion, hence it correlates perfectly with the myocardial blood flow. The short half-life of 2.4 minutes allows measurements to be repeated at short intervals of 10 to 15 minutes.

N-13 ammonia has non-linear uptake, both free diffusion and active first pass extraction. It has a half-life of 10 minutes which allows repeated evaluations of rest and stress myocardial blood flow at longer time intervals (about 30-40 minutes) when compared to O-15 H2O. Assessment of stress perfusion and left ventricular function is also possible

82-Rubidium (Rb-82) has non-linear uptake and active first pass extraction. It has an ultra-short half-life of approximately 1.3 minutes which permits serial imaging during both rest and stress.

The literature reports higher sensitivity and specificity for PET compared to SPECT for the detection of CAD. Importantly, quantitative measurements of myocardial perfusion can play a pivotal role in the detection of balanced ischaemia (281). Quantitative imaging with SPECT, on the other hand, is also becoming available.

- 18F-FDG PET is also used in cardiology for other conditions, for instance for the detection of inflammatory and infectious conditions (e.g. endocarditis and sarcoidosis) and atherosclerosis(281).

5.4 Echocardiography.

Echocardiography is a well-established non-invasive technique which uses ultrasounds waves to produce images. Ultrasound waves are produced by a piezoceramic transducer, which generates an ultrasound beam from an electrical signal. The ultrasound beam will be reflected in different way from the different internal organs and return to the probe with different echocardiography return, which is affected by the tissue composition and

depth. Computed analysis of the transmitted and received signals allows real time anatomical evaluation of the scanned body section(178).

Two-dimensional, three-dimensional, and Doppler ultrasound images are used for the evaluation of the heart. This technique provides information about cardiac function and morphology as well as hemodynamic information if performed during stress (178).

Doppler technique is used for the assessment of the cardiac flows, to study abnormal shunts and valvular pathologies such as regurgitation and stenosis.

The stress technique is a combination of 2D echocardiography with either pharmacological or physical stress. The stress will increase the myocardial oxygen need and territories supplied by arteries with hemodinamically significant CAD will show a worsening in the wall motion (282).

Given that echocardiography is widely available, non-invasive and radiation free, it is routinely performed in ESRD patients as part of their normal cardiac screening. echocardiography plays a big role in this population in fact can provide several important information:

-Evaluation of LVH: as previously described LVH is a common complication in this population and this technique can provide excellent evaluation of the left ventricular volumes and mass with high accuracy for the detection of LVH and the assessment of its geometry (concentric or eccentric) (283).

-Evaluation of left ventricular systolic dysfunction: the prevalence of the LV systolic dysfunction has been reported to be as high as 28% ESRD population (284) and it is an important unfavorable prognostic indicator (285). The echocardiography evaluation of the LV systolic function is performed with methods that evaluate the degree shortening and ejection fraction.

-Evaluation of left ventricular diastolic dysfunction: diastolic dysfunction is characterized by abnormal LV compliance and relaxation, which leads to an increase in the filling pressures. An increase of the LV volume can complicate into acute pulmonary edema and intradialytic hypotension (286, 287) even in presence of normal EF hence it is crucial to identify these abnormalities in early stages.

-Evaluation or left atrial dilatation: left atrium dilatation is a strong predictor of cardiovascular events in the general population (288) such as atrial

fibrillation, cerebrovascular accident, heart failure, myocardial infarction and cardiac death (289). In the ESRD population it has been demonstrated that the atrial dilatation was an independent predictor of mortality in patents on dialysis (290, 291). The assessment of the LA with echocardiography should be done in two-dimensional mode and not by the traditional measurement of the anteroposterior diameter in the M-mode (292, 293).

-Assessment of pericardial disease: Acute pericarditis is a possible complication in ESRD patients and it can be caused by uraemia and/or inadequate dialysis (294). Sometimes drainage is necessary to avoid cardiac tamponade and echocardiography can play an important role in the diagnosis and invasive treatment of this condition.

-Stress Echocardiography: pharmacological stress echocardiography allows the assessment of myocardial ischemia and provides at the same time information about the cardiac function. The presence and extension of the ischemia are independent prognostic values in this population (295)making this technique very appealing also for this group of patients.

Chapter 6: Project Methods

6.1 Study Population, Inclusion and Exclusion Criteria for the Project

The ACHILLES study (REC Ref. 12/LO/0672) was directly supported by the NIHR Cardiovascular Biomedical Research Unit at Barts (Grant no. MCPH1B9T/24ET52), which is supported and funded by the National Institute for Health Research (NIHR).

The primary hypothesis was that CCTA could perform at least as well as MPS in the cardiovascular assessment of this patient population.

The study protocol received Research Ethics Committee approval and all patients gave written informed consent. My involvement in the study consisted in approaching patients, inform them and obtain consent. I was then in charge of organising the CT scanning slots and supervising the scan acquisition. For patient recruitment, I attended the Transplant Assessment Clinic of the Royal London Hospital between October 2012 and March 2014. Patients considered suitable for kidney transplantation were invited to take part in this research study and an information leaflet was given to them. After 3-4 days I would call the patient to discuss again the study, answer their questions, and if they agreed to join the study, I would plan the CCTA in the best day for them, taking into account the dialysis sessions . Exclusion criteria were <18 years of age, known allergy to iodine, unstable clinical condition (haemodynamic or electrical instability), severe systemic illness (e.g. cancer), inability to lie flat and hold the breath for 10 seconds, failure to provide informed consent.

Data on patient symptoms and cardiovascular risk factors were collected prospectively using specific patient questionnaires and were checked with the electronic patient records. Hypertension was defined as having blood pressures higher than 140/90 mmHg or being on treatment for hypertension. Hyperlipidaemia was defined as total cholesterol level of more than 200 mg/dL (5.17 mmol/L). Diabetes was defined as recurrent or

persistent high blood sugar above normal levels [Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl); Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load; glycated haemoglobin (HbA1C) ≥ 48 mmol/mol] Participants were considered to have hypertension, hyperlipidaemia and diabetes if this was recorded in the medical records and if they were on treatment for any of these conditions.

Participants were considered to have family history of cardiovascular disease according to the British Heart Foundation definition (www.bhf.org.uk), if :

- Father or brother was/is diagnosed with cardiovascular disease under the age of 55.
- Mother or sister was/is diagnosed with cardiovascular disease under the age of 65.

Chest pain was defined as follow (296):

Typical chest pain: Meets three of the following characteristics:

1. Substernal chest pain of characteristic quality and duration (usually located near the sternum, or from the epigastrium to the lower jaw or teeth, between the shoulder blades or in either arms and it is described as pressure, heaviness sometimes strangling, constricting, or burning).
2. Provoked by exertion or emotional stress
3. Relieved by rest and/or nitroglycerine (usually lasting less than 10min)

Atypical chest pain meets two of the characteristics described above.

Non-anginal chest pain meets one or none of the characteristics described above.

Patients underwent CCTA (research) as well as MPS (standard of care). Clinical management was based on standard of care investigations (MPS and conventional coronary angiography (CCA), if performed), but it was not mandated by CCTA findings.

Results were reported according to the STARD (297) criteria (Standards for Reporting Diagnostic accuracy studies).

6.2 CAC Score and CCTA Protocols

The CT scans were performed at the London Chest Hospital using a 128-slice second-generation dual-source CT system (Somatom Definition Flash, Siemens Healthcare, Forchheim, Germany) (Scanner's technical feature summarized in table 5; Advantages of dual source technique are discussed in Chapter 4).

Table 5: Technical features of Somatom Definition Flash.

X-Ray tube	2 x Vectron™
Detector	2 x Stellar^{Infinity} detector with 3D anti-scattering. Each Stellar^{Infinity} has 96 detector raws.
Number of slices acquired/rotation	384 (2 x 192)
Rotation time	Up to 0.25 s
Temporal resolution	66 ms
Generator power	240 kW (2 x 120 kW)
kV Steps	70,80.100.120.140 kV
Spatial resolution	0.22 lp/cm (0.24 mm)
Max. scan speed	737 mm/s with Turbo Flash
Table load	Up to 307 kg / 676 Ibs
Gantry opening	78 cm
Imaging reconstruction	Iteractive reconstructions (ADMIRE) Filtered back projection (FBP)

Wherever possible for patients on dialysis treatment we scheduled the CT appointment on the same day prior to the dialysis session, or the day before.

CCTA images were evaluated by an experience consultant who was unaware of the MPS findings.
Patients were instructed to follow the breathing instructions and were rehearsed to hold their breath for approximately 10-12 s before the scan procedure.

Patients with a heart rate >65bpm and without contraindications to beta-blockers (contraindications are: asthma, bradycardia, second or third degree heart block) received 5-35mg of intravenous metoprolol in order to achieve a target heart rate of <65beats/min. Sublingual nitrates were used in patients without contraindications (contraindications are: severe aortic stenosis, glaucoma, low blood pressure, severe bradycardia and the use of phosphodiesterase inhibitors in the last 24-48h).

First, all patients underwent a non-contrast scan for the calculation of the CAC score using the Agatston method. A prospectively ECG-triggered, high-pitch spiral protocol was used. Scan parameters were an X-ray tube voltage of 120kV and a tube current of 75mA.

For CCTA, either a prospectively ECG-triggered or a retrospectively ECG-gated protocols were used, depending on the presence of heart rate irregularities immediately prior to the scan. Both X-ray tubes were operated at a voltage of 100 kV. Scout-based automatic tube current modulation (CareDose 4D, Siemens Healthcare, Forcheim, Germany) was used with the reference tube current–time product set at 370 mAs per rotation. 0.75mm-thick images were reconstructed with a slice increment of 0.5mm.

A volume of 50ml of contrast agent (300 mg/mL, Omnipaque, GE Healthcare, Milwaukee, MI) was injected with an injection rate of 5mL/s into an antecubital vein through a 20-gauge catheter, using a dual-head power injector (Stellant, Medrad, Indianola, USA). Contrast was followed by 40ml of saline with the same injection rate.

A test bolus scan of 10ml of contrast (followed by 30ml of saline) was injected to determine the time to peak enhancement in the ascending aorta. Attenuation changes in the ascending aorta were monitored with low-dose single slice scans obtained at 1s time intervals. The time to peak enhancement, summed to a fixed delay of 3s, was applied as the diagnostic delay to initiate the CCTA acquisition. Scans were performed in a craniocaudal direction, starting below the aortic arch and ending just below the base of the heart.

6.3 Image Reconstruction

CAC score images were reconstructed with a slice thickness of 3 mm, an increment of 1.5 mm, a field of view of 180 mm and a medium-soft convolution kernel (B35). CCTA images were reconstructed with a slice thickness of 0.75 mm, an increment of 0.5 mm, a field of view of 180 mm, a medium-soft convolution kernel (B26) and additionally a dedicated sharp convolution kernel (B46) in patients with detectable coronary calcium.

6.4 Image Analysis

CAC scores were obtained according to standard procedure using commercially available software (syngo Calcium score, Siemens Healthcare). The Agatston score was calculated according to the method described in 3.2. Agatston CAC score results were dichotomised as zero CAC score (Agatston CAC score =0) and positive CAC score (Agatston CAC score >=1). A sub-analysis was conducted in patients with high CAC score (using a threshold of 1000), because heavy diffuse calcifications in the coronary arteries are a known potential challenge to the accurate interpretation of CCTA.

CCTA axial images, multiplanar reformations, and maximum intensity projections were used to evaluate the coronary arteries. Coronary artery segments were classified according to a modified American Heart Association 17-segment model (298). Datasets were evaluated by two independent observers (one with 3 years' experience, one with 10 years' experience). Disagreement was resolved by consensus reading. The severity of coronary artery stenosis was visually assessed using a grading system recommended

by the Society of Cardiovascular Computed Tomography (244) (Table 6). A threshold of ≥50% coronary diameter reduction was used to define significant stenosis/obstructive CAD. Presence of at least one ≥50% coronary stenosis was used to define CCTA as positive.

Table 6 modified from (244). Qualitative coronary artery stenosis grading.

Descriptive Lumen Obstruction	**Stenosis Grading**
Normal	Absence of plaque/no luminal narrowing
Minimal	Plaque with <25% diameter narrowing
Mild	25%–49% diameter narrowing
Moderate	50-69% diameter stenosis
Severe	70%–99% diameter stenosis
Occluded	100% diameter stenosis

Myocardial wall thickness was measured in all study participants at the level of the basal septum, using multiplanar reformation short-axis views of the left ventricle at basal level. A mid-to-end diastolic CT dataset was used. LVH was defined as thickness ≥13 mm, in keeping with echocardiography criteria by the British Society of Echocardiography (299) (Table 7).

Table 7: Modified from (299). Reference limits and values of left ventricular wall thickness.

	Normal	Mild	Moderate	Severe
LV Wall Thickness (mm)	6-12	13-15	16-19	≥20

6.5 Radiation Dose Estimates

To provide estimates of the effective radiation dose associated with CT, the dose-length product (DLP) for each scan was multiplied by a 0.014 conversion factor for the chest (300).

6.6 Myocardial Perfusion Scintigraphy (MPS) Protocol

The MPS studies (standard of care) were performed at the Royal London Hospital using a two days stress first technique. For stress images, adenosine was infused at a dose of 140mcg/kg/min for 6 minutes. Based on the patient's body weight, 250-350 MBq of Tc-99m tetrofosmin/sestamibi were injected 4 minutes into the adenosine infusion. Image acquisition started within 2 hours (ECG-gating, 16 frames/cardiac circle). For the resting images, 750-1000 MBq of Tc-99m tetrafosmin/sestamibi were injected and images were acquired using the same protocol.

6.7 MPS image analysis

Images acquired on both gamma cameras are automatically transferred to the workstation for processing and image analysis. MPS were reported by an experienced consultant who was not aware of the CCTA findings.

MPS was defined as positive when a perfusion defect was identified. A perfusion defect detected on a region that it is normal on the rest images was considered suggestive of myocardial ischaemia. Perfusion defect on both stress and rest images was considered as myocardial infarction.

All images were evaluated by using a 17-segment model in order to match coronary vessels and myocardial territories.

6.8 Statistical analysis

Statistical analyses were performed using commercially available software (SPSS, version 20.0, Chicago, IL, USA). Continuous variables are presented as

mean±SD or median with interquartile range when not normally distributed. The Kolmogoroff-Smirnow test was used to test for normality. Categorical variables are presented as frequencies and percentages and compared using the $\chi 2$ test.

Cigarette smoking was recorded as positive if patients were current smokers.

Diagnostic performance of CAC score and CCTA compared to MPS was evaluated on a per-patient and per-vessel levels and expressed as sensitivity, specificity, positive and negative predictive values, and their corresponding 95% confidence intervals.

The agreement between CCTA and MPS in assessing the presence of LVH was calculated by means of Cohen's kappa statistics. Kappa results for agreement were interpreted as being poor ($\kappa < 0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), good ($\kappa = 0.61–0.80$), very good ($\kappa = 0.81–0.90$), or excellent ($\kappa \geq 0.91$). A P-value of less than 0.05 was considered significant.

Since this was a feasibility study and part of a clinical development programme, formal sample size calculation was not performed. The population sample was established the basis of the expected number of patients attending the renal clinic during the study period.

Chapter 7: Diagnostic Performance of CAC Score in Predicting MPS Perfusion Defects

7.1 Rationale and Aim

The rationale for studying CAC score was introduced in paragraph 3.4. In the ESRD population, CAC score is not a highly specific indicator of atherosclerosis, because medial sclerosis – that is not due to atherosclerosis but is a manifestation associated with uraemia - contributes to total CAC score. Thus in ESRD patients both intimal calcifications related to atherosclerosis and medial calcification related to uraemia will contribute to total CAC score. Both changes can potentially lead to perfusion defects on MPS. Both intimal and medial calcification may also be associated with cardiovascular death and all cause death, although this does not always imply the presence of underlying obstructive luminal CAD (171-174). A baseline zero CAC score is associated with a significant lower rate of cardiovascular events in the ESRD population (113). Hence, zero CAC score is a simple and practical tool to exclude both atherosclerosis and medial sclerosis in the coronary arteries.

The first aim of this thesis (Aim 1) was to evaluate the diagnostic performance of CAC score in predicting MPS perfusion defects as the standard of reference.

7.2 Methods

7.2.1 Population

From October 2012 to March 2014, patients were prospectively enrolled among those referred for cardiovascular screening at the Transplant Assessment Clinic of the Royal London Hospital. The study population, inclusion and exclusion criteria are described in section 6.1.

7.2.2 CAC Score and MPS Protocols

CAC score and MPS were performed in all participants according to the protocols described in section 5.2 (CAC score) and 5.6 (MPS).

7.2.3 Statistical Analysis

As described in 5.8, statistical analyses were performed using commercially available software (SPSS, version 20.0, Chicago, IL, USA). The diagnostic performance of CAC score compared to MPS was evaluated on a per-patient and per-vessel level and expressed as sensitivity, specificity, positive and negative predictive values, and their corresponding 95% confidence intervals.

7.3 Results

7.3.1 Baseline Characteristics

A total of 119 participants received CAC score and MPS. The inclusion procedure of the whole study is detailed in Figure 6.

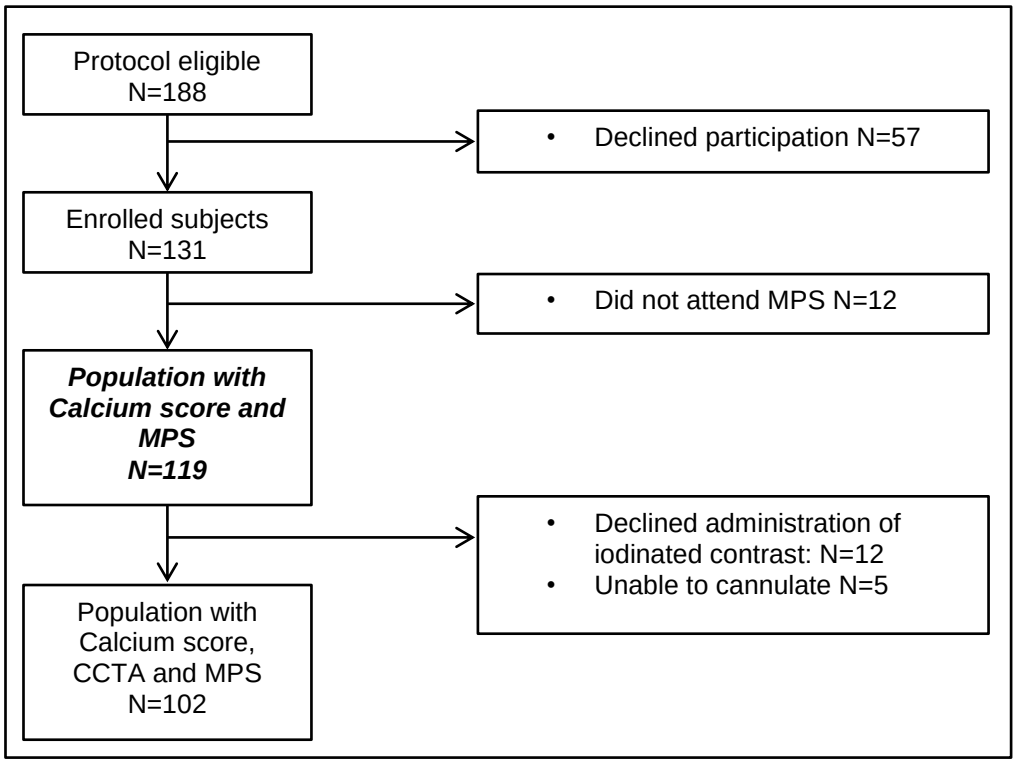

Figure 6 Inclusion procedure.

Baseline clinical characteristics of the 119 participants that underwent CAC score and MPS are shown in the Table 8.

Table 8. Baseline clinical characteristics of 119 patients who underwent CAC score and MPS.

Gender (M/F)	80/39	
Age(Years)	54 ± 10	
Risk Factors for CAD		
Diabetes Mellitus	n: 60	50%
Hypertension	n:107	90%
Hypercholesterolemia	n: 74	62%
Current Smoking	n: 31	24%
Obese (BMI≥ 30 kg/m^2)	n: 28	24%
Family History for CAD	n: 20	17%
Symptoms		
Asymptomatic	n: 104	87%
Dyspnoea	n: 15	13%
Typical chest pain	n: 0	0%
Atypical chest pain	n: 0	0%
Non-anginal chest pain	n: 0	0%
Pretest likelihood of CAD		
Low	n: 119	100%
Intermediate	n: 0	0%
High	n: 0	0%
Dialysis Duration (Months)	24 ± 4	
CAC Score		
Median CAC Score	75 (IOR 396)	
CAC Score 0	n: 38	32%
CAC Score 1-100	n: 8	7%
CAC Score 101-400	n: 19	16%
CAC Score 401-1000	n: 25	21%
CAC Score >1000	n: 29	24%
Participants with MPS Perfusion Defects	n: 26	22%

BMI = body mass index; CAD = coronary artery disease

The data were positively skewed (Kolmogorov–Smirnov test $p<0.01$; Shapiro–Wilk test $p<0.01$) and the median of the calcium score was 75 (0-396), range 0-4603.

The average DLP for calcium score was 26.25 (+/- 9.8).

7.3.2. CAC Score and MPS Perfusion Defects

The median (IQR) CAC score was 53 (0-294) in patients without MPS perfusion defects, and 171 (17-1007) in patients with perfusion defects (p=0.046 from Mann-Whitney test).Among the 119 participants that underwent CAC Score and MPS, 36/119 (30%) participants had a zero-CAC score, of whom 33/36 (92%) had no perfusion defects on MPS. Eighty-three/119 (70%) participants had CAC score >1, of whom 60/83 (72%) had no perfusion defects on MPS (Table 9).

Only 3 participants with zero CAC score had perfusion defect noted on MPS. These 3 participants went on to have CCTA and were found to have moderate LVH without coronary artery plaque on CCTA (Chapter 8).

Table 9: Cross-Tabulation of CAC score vs MPS

	MPS Negative	MPS Positive	Total
CAC Negative	33 (92%)	3 (8%)	36
CAC Positive	60 (72%)	23 (28%)	83
Total	93 (78%)	26 (22%)	119

CAC Score positive is defines as total CAC Score ≥1; MPS Positive is defined as presence of perfusion defects of MPS.

The sensitivity, specificity, PPV and NPV of CAC score in predicting MPS perfusion defects were 88% (CI: 70-97), 35% (CI: 26-46), 28% (CI: 18-39) and 92% (CI: 78-98), respectively.

7.4 Discussion and limitations

The main findings of our study were as follows:

Firstly, only approximately one in five (22%) ESRD patient awaiting a kidney transplant were found to have perfusion defects on MPS. Overall this finding was in agreement with the clinical estimation of the pre-test probability of CAD, which was low. This suggests that the use of a non-invasive test instead of an invasive test appears justified.

Secondly, we found that approximately a third (32%) of the patients had zero CAC score. This finding implies the absence of coronary atherosclerosis as well as the absence of medial sclerosis, and is known to be associated with good prognosis.

CAC score has been extensively validated as a powerful non-invasive imaging modality in the general population. Even in presence of diabetes, a zero CAC score translates into a similar cardiovascular risk to patients without diabetes (158).

In all but three patients, there was agreement between CAC score being zero and MPS being negative for perfusion defects. When CAC score was dichotomised into zero vs. >=1, sensitivity (88%) and NPV (92%) were high, despite lower specificity (35%) and PPV (28%). CAC score is a rapid non-expensive, contrast free and low-radiation dose test. The high NPV found in the low likelihood population included in this study suggests that zero CAC score may be a useful clinical tool in the pre-surgical screening of ESRD population, particularly by identifying patients in whom further testing for significant CAD is not required.

Few promising data were published so far regarding CAC score in the ESRD population showing that CAC score was a good predictor of future coronary events and more importantly a zero CAC score translated into a significantly lower cardiac event rate (113) (discussed in Chapter 3).

We also found that approximately two thirds (68%) of the patients included in this study had CAC score ≥1, but only one fifth had MPS perfusion defects. This suggests that CAC score ≥1 is not reliable to rule-in MPS perfusion defects, no matter if they are the result of atherosclerosis, uraemic changes or both.

CAC score has a further limitation. MPS perfusion defects can result from atherosclerosis, uraemia but also LVH can play a role. As CAC score is a contrast free technique, LVH cannot be assessed reliably due to very poor or absent differentiation between blood pool and myocardium in baseline conditions.

CAC is also limited because it is not a specific test to discriminate between the two different pathophysiological processes such as uraemia and atherosclerosis, both leading to vascular calcifications.

We could not demonstrate statistically significant differences in CAC score in patients with different baseline characteristics, such as for instance presence vs. absence of diabetes, hyperlipidaemia and cigarette smoking. Similarly, the, relationship between CAC score and dialysis duration did not reach statistical significance. Studying the effect of these variables on CAC score, however, was beyond the purpose of our study, which was not sufficiently powered for these analyses.

Also, we have not studied imaging findings in relation with any circulating biomarkers. Of note, no circulating biomarkers are currently available for the reliable dectection of ischaemia in patients with stable CAD.

A further limitation of this study was the lack of comparison with a reference standard. This was discussed with the clinical and research teams when designing this study, and it was felt it would have been unethical to perform invasive coronary angiogram in all patients for research purposes, even

when not clinically indicated, due to the risks associated with intra-arterial puncture and contrast injection.

Chapter 8: Diagnostic Performance of CCTA in Predicting MPS Perfusion Defects

8.1 Rationale and Aim

CCTA is an established non-invasive test to assess CAD. The strength of CCTA lays in its high negative predictive value (234) i.e. the excellent ability to rule out the presence of obstructive CAD. This applies to both stable chest pain patients and low-risk patients with suspected acute coronary syndromes(183).

Promising but little data have been published regarding the use of CCTA in the ESRD population. The stigma that ESRD patients have heavily calcified coronary arteries has limited the research and clinical applications of CCTA in these patients. Few studies, however, reported that CCTA was safe to perform in asymptomatic ESRD patients (174) and had encouraging diagnostic performance, both at a patient and vessel level (301, 302). Data reported in this thesis (Chapter 6) showed that approximately one in three ESRD patients did not have any coronary calcifications.

Given the aforementioned limitations of CAC scoring in ESRD patients, particularly the notion that vessel calcification can be the result of separate processes such as atherosclerosis and medial sclerosis, as well as the fact that perfusion defect may be secondary to uraemic changes and LVH and not only to epicardial coronary artery stenosis from CAD, we hypothesised that CCTA may be more helpful and accurate than CAC score to rule-out epicardial coronary stenosis from CAD, especially in patients with CAC score >=1.

By providing anatomical imaging of the coronary arteries, CCTA should be capable of identifying those patients for whom revascularisation of CAD is potentially beneficial. CCTA can exclude CAD and be of reassurance for those patients for whom invasive assessment with catheter coronary angiography is unnecessary.

Our finding that only one in five kidney transplant candidates had perfusion defects on MPS (Chapter 6) confirmed that a diagnostic tool of non-invasive nature was appropriate in this context, because the expected prevalence of perfusion defects in this population was rather low.

The second aim of this thesis (Aim 2) was to evaluate the diagnostic performance of CCTA in detecting obstructive CAD as a predictor of MPS perfusion defects, with the latter as the standard of reference.

8.2 Methods

8.2.1 Population

From October 2012 to March 2014, patients were prospectively enrolled among those referred for cardiovascular screening at the Transplant Assessment Clinic of the Royal London Hospital. Inclusion and exclusion criteria were discussed in section 5.1.

We used a CAC score value of 1000 as a threshold to arbitrarily define patients with high coronary calcification. This widely accepted clinical threshold was used to divide the study population in patients with high (>1000) and low (between 1 and 1000) CAC score. We evaluated the performance of CCTA in predicting MPS perfusion defects in patients without any calcification i.e. zero CAC sore, with high and low CAC scores.

8.2.2 CCTA and MPS Protocol

CCTA and MPS were performed in all participants according to the protocol described in section 5.2 (CCTA) and 5.6 (MPS).

8.2.3 Statistical Analysis

The diagnostic performance of CCTA compared to MPS was evaluated at the patient and vessel level and expressed as sensitivity, specificity, positive and negative predictive values, and their corresponding 95% confidence intervals. The agreement between CCTA and echocardiography in assessing the presence of LVH was evaluated by calculation of Cohen's kappa statistics, as described in section 5.8.

8.3 Results

8.3.1 Baseline Characteristics

A total of 102 participants underwent CCTA and MPS. Data on CAC score were also available in these patients (Inclusion procedure shown in Figure 6). The baseline characteristics of the 102 participants that underwent CCTA and MPS are shown in Table 10.

Table 10: Baseline characteristics of 102 patients who underwent CCTA and MPS.

Gender (M/F)	69/33	
Age(Years)	53 ± 10	
Risk Factors for CAD		
Diabetes Mellitus	n: 50	49%
Hypertension	n: 90	88%
Hypercholesterolemia	n: 61	60%
Current Smoking	n: 27	26%
Obese (BMI≥ 30 kg/m^2)	n: 21	21%
Family History for CAD	n: 15	15%
Symptoms		
Asymptomatic	n: 87	85%
Dyspnoea	n: 15	15%
Typical chest pain	n: 0	0%
Atypical chest pain	n: 0	0%
Non-anginal chest pain	n: 0	0%
Pretest likelihood of CAD		
Low	n: 102	100%
Intermediate	n: 0	0%
High	n: 0	0%
Dialysis Duration (Months)	34 ± 5	
Participants with MPS Perfusion Defects	n: 23	23%
Participants with Positive CCTA	n: 23	22%

BMI = body mass index; CAD = coronary artery disease

Ninety/102 (88%) patients had echocardiography. LVH (defined according to the criteria of British Society of Echocardiography, as in section 5.4) was detected in 46% of the population (n=47/102). There was excellent agreement between CCTA and Echocardiography in identifying LVH (K=1; P=.000).

All but 1 patients among the 102 underwent CCTA with prospectively ECG-triggered protocol. Only one patient was scanned with retrospectively ECG-gated protocol due to an irregular heart rate. The average DLP for the whole population was 404 (+/- 170).

8.3.2 Diagnostic Performance in the Entire Population

No adverse events were recorded during or after CCTA. Among the 102 participants who underwent CCTA and MPS, 79/102 (77%) participants had negative CCTA, of whom 69/79 (97%) had no perfusion defects on MPS. Twenty-three/102 (22%) participants had positive CTCA, of whom 13/23 (56%) had perfusion defects on MPS (Table 11).

Ten/79 (13%) participants with negative CTCA had perfusion defects noted on MPS. Of these patients, 7/10 (70%) had LVH.

Table 11: Cross-Tabulation of CCTA vs MPS

	MPS Negative	MPS Positive	Total
CCTA Negative	69 (87%)	10 (13%)	79 (78%)
CCTA Positive	10 (44%)	13 (56%)	23 (22%)
Total	79 (78%)	26 (22%)	102

CCTA positive is defines as coronary artery narrowing ≥ 50%; MPS Positive is defined as presence of perfusion defects of MPS.

Overall the sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the patient level were 55% (CI: 35-77), 87% (CI: 78-94), 57% (CI: 35-77) and 87% (CI: 78-94), respectively.

The sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the vessel level were 48% (CI: 31-66), 92% (CI: 88-95), 41% (CI: 26-58) and 94% (CI: 90-96), respectively.

8.3.3 Patients with Zero CAC Score

Zero CAC score was found in 32/102 (31%) of the participants who underwent CTCA (Figure 7).

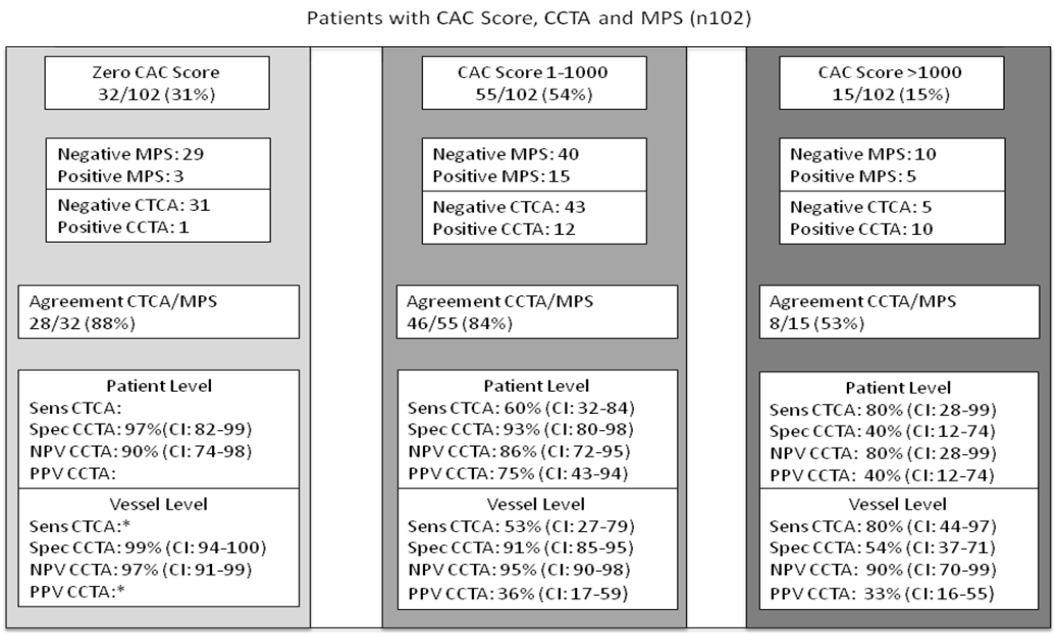

Figure 7: *Sensitivity and PPV could not be calculated due to the small sample size

In patients with zero CAC score, 31/32 (97%) had negative CCTA. In patients with zero CAC score, 28/32 (88%) had both negative CCTA and no perfusion defects on MPS. No participants with zero CAC score were found to have both positive CCTA and perfusion defects on MPS (Table 12). Three patients with zero CAC score had perfusion defects on MPS (and negative CCTA). All of these three patients had moderate LVH, which was echocardiographically confirmed.

Only 1/32 participant had positive CCTA, but no perfusion defects on MPS.

Table 12: Cross-Tabulation of CCTA vs. MPS in the population with zero CAC Score

	MPS Negative	MPS Positive	Total
CCTA Negative	28 (90%)	3 (10%)	31 (97%)
CCTA Positive	1 (100%)	0 (0%)	1 (3%)
Total	29 (91%)	3 (9%)	32

CCTA positive is defines as coronary artery narrowing ≥ 50% ; MPS positive is defined as presence of perfusion defects of MPS.

The specificity and NPV of CCTA in predicting MPS perfusion defects at the patient level were 97% (CI: 82-99) and 90% (CI: 74-98), respectively. The specificity and NPV of CCTA in predicting MPS perfusion defects at the vessel level were 99% (CI: 94-100) and 97% (CI: 91-99), respectively. Sensitivity and PPV could not be calculated due to the small sample size.

8.3.4 Patients with Positive CAC Score

Positive CAC score (CAC score >=1) was found in 70/102 (69%) of the participants (Figure 7). In these patients, 22/70 (31%) had positive CCTA and 48/70 (69%) had a negative CCTA. Among the positive CTCA's, 13/22 (59%) had perfusion defects and 9/22 (41%) did not. Among the negative CTCA's, 41/48 (85%) had no perfusion defects and 7/48 (15%) did. These 7 patients were found to have echocardiographically confirmed LVH.

Only 13/70 (18%) patients had both positive CCTA and positive MPS. In 41/70 (59%) patients, despite positive CAC score, CCTA and MPS were both negative (Table 13).

Table 13: Cross-Tabulation of CCTA vs MPS in the population with positive CAC score

	MPS Negative	MPS Positive	Total
CCTA Negative	41 (85%)	7 (15%)	48 (69%)
CCTA Positive	9 (41%)	13 (59%)	22 (31%)
Total	50 (71%)	20 (29%)	70

CCTA positive is defined as coronary artery narrowing ≥ 50% ; MPS positive is defined as presence of perfusion defects of MPS.

The sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the patient level were 65% (CI: 41-85), 82% (CI: 69-92), 50% (CI: 36-79) and 85% (CI: 72-94) respectively.

The sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the vessel level were 48% (CI: 31-67), 87% (CI: 81-92), 40% (CI: 24-57) and 91% (CI: 85-95), respectively.

8.3.5 Patients with High and Low CAC Score

In patients with high CAC score (>1000; n=15), 5/15 (33%) had MPS perfusion defects (Figure 7). In these patients there was poor agreement between CCTA and MPS, with only 8/15 (53%) cases in agreement at the patient level.

In patients with low CAC score (between 1 and 1000; n=55), 15/55 (27%) had MPS perfusion defects. In these patients, however, agreement between CCTA and MPS results was found in 46/55 (84%) patients (Table 14).

Table 14. Agreement between CCTA and MPS using CAC Score threshold value of 1000

	Total within group	Both Positive	Both Negative	Total Agreement	% agreement
CAC 1-1000	55	9	37	46	84%
CAC >1000	15	4	4	8	53%
Total	70	13	41	54	

Thirty-seven/55 patients (67%) of the participants with low CAC score and negative CCTA had no perfusion defect on the MPS.

In 11/55 (20%) participants with a low CAC score there was disagreement between CCTA and MPS results. Particularly 3 participants had a positive CCTA and no perfusion defects on the MPS, of whom 2 had a coronary angiography that confirmed the CCTA findings. Both participants had two vessel disease on CCTA. Seven participants had perfusion defects on the MPS and no significant coronary stenosis detected on the CCTA; in 6 of these patients there was moderate or severe LVH. Three of these patients had a coronary angiography that confirmed the CCTA findings.

Only 13 patients had coronary angiography .Coronary angiography was not systematically performed as part of the study protocol, as this was not deemed ethical and was not included in the study design.

In patients with low CAC score, sensitivity, specificity, PPV and NPV of CCTA at the patient level were 60% (CI: 32-84), 93% (CI: 80-98), 75% (CI: 43-94) and 86% (CI: 72-95), respectively.

The sensitivity, specificity, PPV and NPV of CCTA in predicting MPS perfusion defects at the vessel level were 53% (CI: 27-79), 91% (CI: 85-95), 36% (CI: 17-59) and 95% (CI: 90-98), respectively.

8.4 Discussion and limitations

The main findings of our study were as follows:

Firstly, approximately one in five (23%) patients had perfusion defects on MPS. One in five patients had positive CCTA (23%). This confirmed the population had a low prevalence of coronary artery disease, hence the preference of non-invasive testing over invasive testing as a screening tool may be appropriate.

We divided this population in groups according to the presence of coronary calcium detected on the CAC Score. Hence, there was a zero CAC score group, and among patients with positive CAC score, a low CAC score group (1-1000) and a high CAC score group (>1000).

Patients with zero CAC Score

In this patient group, the ability of CCTA to exclude perfusion defects was excellent (97% specificity, 90% NPV at the patient level and 99% specificity, 97% NPV at the vessel level).

Sensitivity and PPV in this group could not be estimated due to the very small number of patients with demonstrated perfusion defects (true positives). In this group, CCTA performed after CAC score did not lead to reclassification of any participants. Thus it could be argued that CCTA could be avoided in patients with zero CAC score. An approach in favour of CAC score used as a gate-keeper prior to CCTA was supported by the recently updated 2010 NICE guidance (303) on the investigation of stable chest pain of recent onset. According to this document, no further testing was recommended in patients with zero CAC score. Although it has been shown that non-calcified atheroma could be responsible of coronary stenosis in up to 3-4% of cases (222), the patients included in this study were free from ischaemic symptoms and received a cardiac investigation in the setting of screening for coronary artery disease prior to kidney transplantation. The finding of zero CAC score excluded both endothelial calcifications

from atherosclerosis and medial calcifications from uraemic vascular disease. These findings appear quite reassuring in this context, and may practically obviate the need of further testing. This particularly applies to patients with CKD and ESRD, where the injection of iodinated contrast agent may be associated with higher risk of nephrotoxicity compared patients withour CKD.

Patients with positive CAC score

The diagnostic performance of CCTA in predicting MPS perfusion defects was moderate in patients with a positive CAC score.

The effect of coronary calcification in influencing the diagnostic performance of the CCTA is a well known phenomenon (301). Coronary calcifications cause partial volume averaging artefacts that translate in the visual "blooming effect". This means calcifications appear larger than their actual size on the CT image, and by doing so prevent the accurate evaluation of the vessel lumen for the presence of luminal stenosis. As a consequence of this phenomenon, the coronary arteries may not be accurately evaluable for the presence of stenosis, or there can be a tendency to overestimate the severity of luminal stenosis leading to false positive diagnoses. This is typically reflected by a low PPV. Conversely, CCTA is more robust in ruling out coronary stenosis, typically reflected by better NPV.

In patients with high CAC score, defined by an threshold of 1000 Agatston score (304), CCTA showed very poor agreement (53%) compared to the reference standard MPS. Whilst the NPV to exclude disease was moderate, the positive predictive value was exceedingly low (40%).

However, in patients with low CAC score (between 1 and 1000), the agreement between CCTA and MPS was better (84%) and the PPV

improved (75%). In this subgroup, the observed prevalence of MPS perfusion defects was still low (27%) justifying the use of non-invasive CCTA as opposed to direct referral to invasive coronary angiography. CCTA may be useful to rule-out CAD, given the low prevalence encountered in this population and given its robust NPV. This is not dissimilar to what has been previously observed in symptomatic patients with stable chest pain and no CKD (305). However, the ability of CCTA to rule in CAD, when the test outcome is positive, may be significantly lower.

In the patients who had unobstructed coronary arteries on CCTA and perfusion defects on MPS, CCTA identified LVH, which was confirmed echocardiographically in all cases, as a potential explanation for the underlying perfusion defects. Myocardial and LVH evaluation using the CCTA dataset may provide additional value for the risk assessment of patients with advanced kidney disease and uraemia (302).

CCTA is not free from limitations. CCTA requires an intravenous injection of iodinated contrast agent, although a small volume (50-60ml, or even less with state-of-art technology) may suffice. This can represent a serious issue in pre-dialysis patients with severely impaired kidney function, and in dialysis patients as well, as residual renal function can be affected. Although this did not occur in our study, CCTA can be inconclusive in patients with fast and irregular heart rates. CCTA involves the exposure to ionising radiation. With latest generation scanners, however, the effective dose is roughly comparable or lower than the annual background exposure from natural sources, and can be significantly lower than that associated with MPS. Also, CCTA can exclude coronary stenosis, but cannot accurately assign ischaemic or haemodynamic significance to coronary stenoses, especially of intermediate severity (e.g. 50-70% diameter reduction). In these cases, testing for inducible ischaemia may still be required. Our study was designed as part of a clinical development programme and we did not plan the systematic use of invasive coronary angiography, which remains the

standard for the evaluation of coronary artery disease, in our study participants. Coronary angiography was performed in patients with positive findings on non-invasive testing and where clinically indicated. Given our population had no ischaemic symptoms (screening settings), a low expected prevalence of coronary artery disease and a major comorbidity such as ESRD, use of systematic invasive angiography for research purposes would have been difficult to justify. This mainly relates to the increased risks secondary to the intraarterial injection of iodinated contrast, which is required for invasive coronary angiography. Iodinated contrast when injected in the arterial circulation may increase the risk of contrast induced nephropathy compared to an intravenous injection such as that used for CCTA (306). The comparison of CCTA (ie. an anatomical test for CAD) with MPS (ie. a functional test for ischaemia) represents a limitation of this study. In view of the above mentioned constraints on the use of invasive coronary angiography, however, MPS remains the most established and widely used reference test used for the cardiovascular screening of kidney transplant candidates in clinical practice. For this reason it was chosen for this study.

Chapter 9: Summary of the Thesis and Future Perspectives

9.1 Summary of the Thesis and future work.

The aim of this work was to compare a novel screening approach based on CT, ie. CAC score and CCTA with MPS in the diagnosis of CAD in patients with ESRD. We evaluated the diagnostic performance of this approach using MPS as the standard of reference.

We chose CT because it is an established imaging test with proven reliability in the evaluation of patients with chest pain from suspected CAD. In this thesis, we applied cardiac CT in a population of asymptomatic ESRD patients to screen for CAD during routine pre-transplant assessment.

MPS is the traditionally used test as it is widely available, well established and it is based on the assessment of ischaemic changes in the myocardium during dynamic exercise or more commonly during pharmacologic stress.

We found that CAC scoring and CCTA were feasible and of potential clinical utility in the setting of cardiovascular risk assessment in ESRD patients.

The role of CAC score in risk stratification and its prognostic value are well known, hence this test has been used for cardiovascular risk assessment in the general population (Refer to section 3.3).

Our data, as well as a previously published study (174), have shown that a third of ESRD patients have zero CAC score, which makes the chance of having significant coronary artery stenosis very unlikely. Zero CAC score is associated with a significant lower rate of cardiovascular events in the ESRD population (113). Our results and other studies suggested that CAC score can be considered a diagnostic option in the asymptomatic ESRD population where further testing can be avoided if the test shows no calcium in the coronary arteries (169, 174).

In patients with calcifications, CCTA could be helpful unless calcifications were so bulky to prevent the evaluability of the vessels. In both general population (refer to section 4.2.1) and in ESRD patients (252-254) CCTA has an excellent NPV (virtually 100%) in the exclusion of CAD. Our study showed that in approximately 59% of patients (Figure 9) CCTA was helpful to rule

out disease. In patients with severe calcifications, CCTA has lower ability to discriminate between patients with CAD vs. without CAD, suggesting that CCTA is not a valid replacement to MPS in these situations.

In summary (Figure 8), we suggest that a negative CAC score can identify patients who do not need further imaging. Given a positive CAC score, CCTA can be performed instead of MPS but only for CAC score <1000. Given the high NPV of CCTA in excluding MPS perfusion defects in this group we believe that there is no need for further imaging if a patient has a negative CCTA (<50% diameter reduction).
If the baseline CAC score is > 1000, patients still need a functional test, as CCTA is not able to predict MPS perfusion defects. Nevertheless, even in this group, the identification of very high CAC can be considered important additional information to plan patient management.

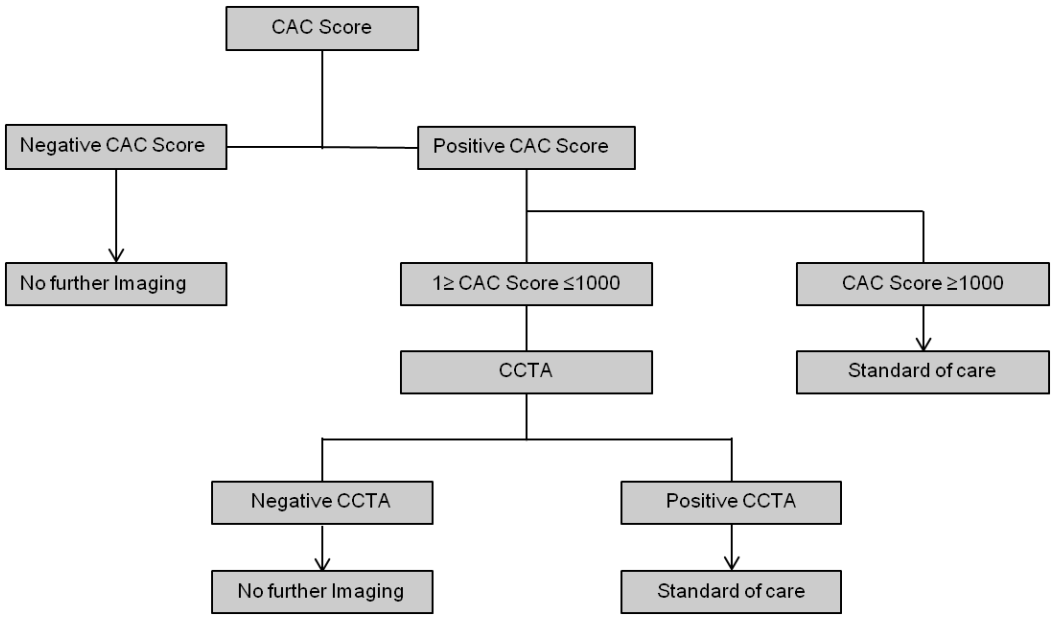

Figure 8. Imaging Approach based on CAC score results.

This novel approach has several benefits for patients:
If no coronary calcium is found then there is no need for the administration of any intravenous contrast, the acquisition time is very short (<5 minutes) and more importantly an extremely low radiation dose (effective radiation dose below 0.5 mSv in our study) is used. If CCTA is performed (positive CAC

score but <1000), an injection of intravenous iodinated contrast is required. We have used a low contrast protocol in order to minimise the risk of CIN and volume overload in this group of patients. As discussed previously (refer to section 4.5), we performed CCTA as close as possible to the next dialysis session (the day before or the same day) and no adverse events were recorded after CCTA.

The strength of CCTA+CAC score is to rule out significant epicardial coronary stenosis but micro-vascular disease cannot be excluded. An MPS perfusion defect may also be uraemia-related micro-vascular disease. In clinical practice there is no invasive procedure to treat micro-vascular disease, but only medical treatment and correction of risk factors. Knowing that there is no significant stenosis in the major epicardial coronary arteries may avoid unnecessary coronary angiography even in cases in which there are MPS perfusion defects related to micro-vascular disease and/or uraemic changes.

This novel approach, if used in clinical practice, can be beneficial for a good percentage of patients (Figure 9):

- In 30% of the patients a negative CAC score excludes MPS perfusion defects.
- In 59% of the patients with a positive CAC score, CCTA can still exclude MPS perfusion defects.
- A CAC Score ≥ 1000 identifies patients who do not benefit from CCTA.

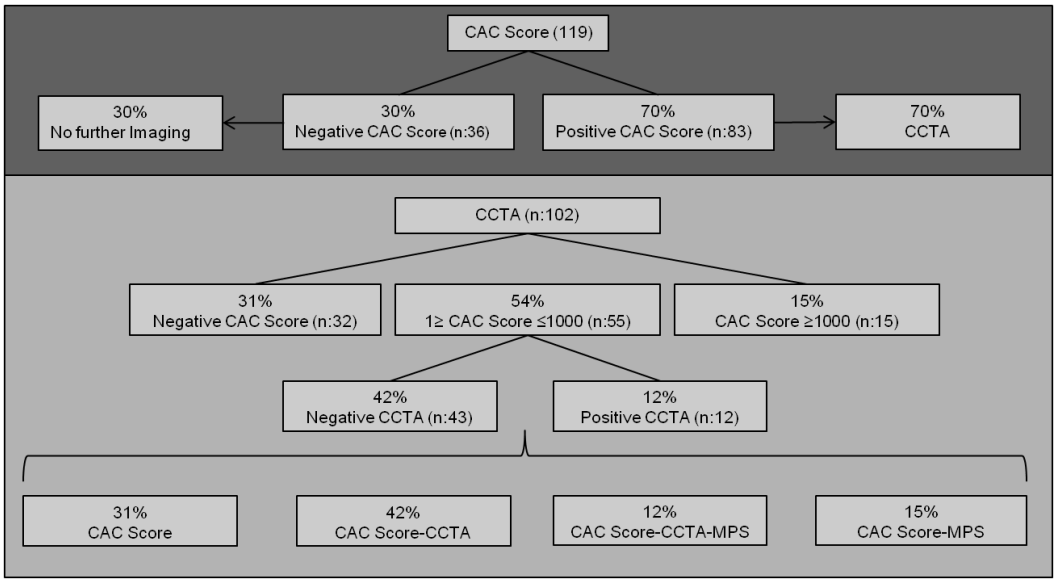

Figure 9. Advantages of this novel approach.

Normally, as routine cardiovascular assessment, transplant candidates also undergo ECG and echocardiography. Given the excellent agreement between echocardiography and CCTA in the detection of LVH, CCTA can be regarded as capable of identifying major myocardial and valvular structural abnormalities. Using a dedicated, retrospectively ECG-gated protocol, CCTA can also evaluate the LV ejection fraction.

Future work:

- Bone metabolic changes and coronary calcification: We would like to further investigate the relationship between CAC score, bone metabolites in the serum and bone mineral density detected by CT .
- Follow-up: a 5-year clinical follow up is planned, which was beyond the life span of this PhD project.
- Further imaging studies with larger populations are necessary to investigate further the usefulness and accuracy of CCTA in this population.
- Novel imaging techniques such as native T1 mapping in CMR and pseudo-equilibrium CT could be applied to evaluate the extra-cellular volume fraction in patients with ESRD as a substrate of

uraemic cardiomyopathy. These novel imaging biomarkers may be prognostically relevant and even help optimise the timing of the transplant.

9.2 Future perspectives and hybrid imaging

CT technology is evolving from a merely anatomical test to a more complete, anatomo-functional test. A functional test would complement the anatomical information on coronary artery stenosis with functional information on either lesion-specific ischaemia secondary to CAD stenosis, or ischaemic changes present downstream in the myocardium due to tissue changes or remodelling. Several approaches have been proposed to do extrapolate functional information on iscahemia based on CCTA:

Transluminal attenuation gradient (TAG) is the contrast opacification gradient through the coronary artery on CCTA. This technique is based on the concept of the fall off of the contrast opacification in the distal coronary artery beyond the significant stenosis and this could potentially be used to better classify lesions(307). At present results regarding TAG are conflicting and this new technique has not yet been validated for clinical use (307-310).

Plaque characteristics can also provide additional important information when combined to plaque stenosis. It has been shown that the presence of low-density plaque component is indicative of necrotic plaque core which is associated with local inflammation and endothelial dysfunction(311). This results in local vasoconstriction and inadequate response to vasodilatation despite the grade of stenosis, with inability of the vessel segment to dilate adequately during stress (311). Given that plaques with necrotic cores are the main cause of myocardial infarction and sudden cardiovascular death (312) the possibility to identify them can be extremely useful in the management of patients. Dedicated software can provide plaque analysis identifying calcified, non calcified plaques and also low-density non calcified plaques and can be an additional help to discriminate ischaemia compared with stenosis evaluation alone (313).

FFR-CT is a parameter computationally derived from CCTA by applying a model representing the resistance to flow during simulated hypaeremia in

each coronary branch. A FFR-CT ≤0.80 is considered to be diagnostic of lesion-specific ischaemia. Several studies have been published suggesting that the diagnostic accuracy of FFR-CT may be superior and additive to CCTA alone in identifying ischaemia-causing lesions and reducing the rates of false positive lesions incorrectly classified by stenosis alone (314, 315). In the NXT trial (316) more sophisticated and new software packages were used and the specificity of FFR-CT was found to be markedly better than in previous studies. The recent multicenter PLATFORM trial (317) compared the effect of FFR-CT-guided testing versus standard diagnostic evaluation on clinical outcomes, resource utilisation, costs, and quality of life in patients suspected of CAD. The authors found that the strategy of using CT angiography with FFR-CT to evaluate patients with suspected CAD was associated with lower costs than a strategy based on invasive coronary angiography and it was also associated with a better quality of life when compared to other non-invasive tests. The main limitation of this technique was the need to transfer CT data for external processing and analysis but recent innovation and the use of new software can now allow the on-site analysis at a regular imaging workstation (318).

Myocardial perfusion imaging (MPI) using computed tomography has become available recently. The detection of myocardial perfusion defects with CT is based on imaging the myocardium post contrast injection during the phase of peak myocardial enhancement, during infusion of a pharmacological stressor, to demonstrate a mismatch between the myocardial blood supply and demand. The main advantage of this is the possibility of evaluating the coronary artery anatomy and pathology and at the same time test the functional significance of a potential coronary stenosis (319). This technique can be particularly useful in the intermediate coronary lesions (30-70% diameter reduction) where it is difficult to predict ischaemia with the anatomical data only (320). Disadvantages are represented by the need of pharmacological stressor injection and an additional contrast injection.

Hybrid Imaging

The main advantage of hybrid imaging is to provide in one dataset of images, anatomical information provided by CCTA and functional information provided by nuclear medicine and in this way by using both datasets, there is a reduction in equivocal results (321).

Hybrid anatomical and functional imaging can help identify the emodinamically significant stenosis by providing information about myocardial territories and their subtending coronary arteries (322, 323).

It has been reported that 201Tl SPECT/64-row MDCT has a better diagnostic performance than CCTA alone in detection 50% stenosis using ICA as standard of reference (324). In particular, the authors found that the hybrid technique not only has the high sensitivity and NPV of CCTA but shows a significant increase in specificity (from 80 to 92%) and PPV (from 69 to 85%) when compared to CCTA alone (324).

Kajander et al. (325) compared PET/CT with invasive coronary angiography in patients with stable chest pain with moderate pre-test likelihood of CAD. Even though both tests were excellent in the exclusion of significant CAD, the hybrid PET/CT imaging was more accurate that both techniques when used alone.

The data available so far indicate that hybrid imaging offers incremental diagnostic value in patients at intermediate risk for CAD by improving not only the identification of the culprit vessel but it also helps to categorize correctly the intermediate lesions and equivocal perfusion defects(326).

List of Figures and Tables

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Publications

- 9 publications in scientific journals
- 12 chapters in scientific volume
- 6 abstracts presented at conferences
- 4 poster sessions presented at conferences
- 2 oral presentations at international conference

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Contributions to Chapters in book

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1. Part I - Fundamentals of Cardiac CT: Cardiac CT basics. Maffei, Palumbo, Martini, Dijkshoorn, Capuano, Weustink, Mollet, Cademartiri
2. Part I - Fundamentals of Cardiac CT: How to optimize Cardiac CT images. Weustink, Rengo, Capuano, Cademartiri, Mollet
3. Part II - Spectrum of diseases: Coronary calcium & plaques . Neefjes-Vermunt, Weustink, Capuano, Rengo, Cademartiri, Mollet
4. Part II - Spectrum of diseases: Coronary stenosis. Meijboom, Neefjes-Vermunt, Weustink, Capuano, Cademartiri, Mollet
5. Part II - Spectrum of diseases: Coronary stents. Pugliese, Capuano, Neefjes-Vermunt, Rengo, Cademartiri, Mollet
6. Part II - Spectrum of diseases: Coronary artery bypass grafts. Weustink, Capuano, Neefjes-Vermunt, Palumbo, Maffei, Cademartiri, Mollet
7. Part III - Clinical applications of cardiac CT & Cases: Cases: Primary prevention. Palumbo, Maffei, Martini, Capuano, Rossi, Dijkshoorn, Cademartiri
8. Part III - Clinical applications of cardiac CT & Cases: Cases: Atypical chest pain. Palumbo, Maffei, Martini, Capuano, Pugliese, Cademartiri
9. Part III - Clinical applications of cardiac CT & Cases: Cases: Stable angina & Chronic chest pain. Rengo, Capuano, Neefjes-Vermunt, Weustink, Cademartiri, Mollet

10. Part III - Clinical applications of cardiac CT & Cases: Cases: Acute Coronary Syndrome. Capuano, Weustink, Rossi, Dijkshoorn, Cademartiri, Mollet

11. Part III - Clinical applications of cardiac CT & Cases: Cases: Secondary prevention. Weustink, Pugliese, Capuano, Rossi, Dijkshoorn, Mollet

12. Part III - Clinical applications of cardiac CT & Cases: New Horizons in Cardiac CT technology. Capuano, Dijkshoorn, Rossi, Cademartiri, Mollet

Abstracts presented at conferences

1 Coert Metz, Michiel Schaap, Stefan Klein, Lisan Neefjes, Ermanno Capuano, Carl Schultz, Robert Jan van Geuns, Patrick W. Serruys, Theo van Walsum, Wiro J. Niessen: Patient Specific 4D Coronary Models from ECG-gated CTA Data for Intra-operative Dynamic Alignment of CTA with X-ray Images. MICCAI (1) 2009: 369-376

2. A.Rossi, W.B. Meijboom, L.A. Neefjes, E. Capuano, N. Mollet, G.P. Krestin, P.J. de Feyter, A.C. Weustink. Accuratezza diagnostica dell'ECG da sforzo e della scintigrafia miocardiaca nella diagnostica della malattia coronarica: confronto "head to head" con l' angiografia coronarica con tomografia computerizzata. SIRM 2010

3. A.Rossi, L.A. Neefjes, E. Capuano, P.J. de Feyter, G.P. Krestin, N. Mollet. Acquisizione spirale "high-pitch" vs acquisizione "step and shoot" in angiografia coronarica con TC a doppia sorgente di seconda generazione: qualita' dell'immagine e dose. Risultati preliminari.. SIRM 2010

4. E Maffei, MD, Parma, PR ITALY; C Martini, RT; E Capuano, MD; S Seitun, MD; A Clemente, MD; F Cademartiri, MD, PhD. Prognostic Value of CT Coronary Angiography: Focus on Obstructive vs Nonobstructive Disease and on the Presence of Left Main Disease. RSNA 2010.

5. E Maffei, MD, Parma, PR ITALY; C Martini, RT; E Capuano, MD; S Seitun, MD; A Clemente, MD; F Cademartiri, MD, PhD.) Cardiac Magnetic Resonance: Delayed Enhancement of the Right Ventricle in Patients with Left Ventricle Primary Involvement. RSNA 2010.

6. C Martini, RT, Parma, ITALY; E Maffei, MD; E Capuano, MD; G Messalli, MD; A Clemente, MD; F Cademartiri, MD, PhD.) Left and Right Ventricle Assessment with Cardiac CT: Validation Study vs Cardiac MRI. RSNA 2010.

Conference poster presentations:

1. Capuano E, Rossi A, Maffei E, Martini C, Cademartiri F (Parma). La TC Del Cuore Con Dose <1msv: Impatto Delle Ricostruzioni Iterative. SIRM 2010
2. Capuano E, Maffei E, Martini C, Rossi A, Cademartiri F (Parma). La TC Del Cuore A Bassa Dose: Approfondimento Sulle Strategie A Seconda Dell'indicazione Clinica E Delle Caratteristiche Del Paziente. SIRM 2010.
3. Capuano E, Maffei E, Martini C, Rossi A, Cademartiri F. La TC Del Cuore Con Dose <1msv: Impatto Della Tecnologia Dual Source Abbinata All'algoritmo Di Scansione Con Triggering Ecg-Prospettico Spirale Ad Alto Pitch. SIRM 2010.
4. A.Rossi, L.A. Neefjes, Marcel Dijkshoorn, E. Capuano, G.P. Krestin, N. Mollet. Angiografia coronarica con TC a doppia sorgente di seconda generazione: selezione ed ottimizzazione dei protocolli di esame. Sirm 2010.
5. Maffei E, Martini C, Arcadi T, Seitun S, E. Capuano, I. Romano, Clemente A, Lario C, Cademartiri F. Parma/IT. Ascending aorta and CT angiography: impact of demographics and cardiovascular risk factors on diameter and area. ECR2011 – Vienna.
6. Maffei E, Martini C, Arcadi T, Seitun S, E. Capuano, I. Romano, Clemente A, Lario C, Cademartiri F. Parma/IT.Acute chest pain of suspected cardiac origin: diagnostic accuracy of calcium score and computed tomography coronary angiography. ECR2011 – Vienna.

Oral presentations at international conference

SCMR 2013: Why Is This Nurse Still Breathless after His Primary PCI? Should We Open It or Close It?. (Society for Cardiovascular Magnetic Resonance Conference San Francisco February 2013).

SCMR 2013: Is Stress CMR Useful in the Management of a Patient with Severe CAD? (Society for Cardiovascular Magnetic Resonance Conference San Francisco February 2013).

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